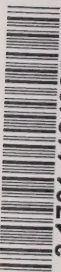


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ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.

Hearing held
8th floor
180 Dundas Street West
Toronto, Ontario

SPIELBERG

In Ch (cont'd)

The Honourable Mr. Justice S.G.M. Grange

P.S.A. Lamek, Q.C.

E.A. Cronk

Thomas Millar

Commissioner

Counsel

Associate Counsel

Administrator

X: Roland

Transcript of evidence
for

October 25, 1983.

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ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

Hearing held on the 8th Floor,
180 Dundas Street West, Toronto,
Ontario, on Tuesday, the 25th
day of October, 1983.

- - - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOT - Registrar

- - - - -

APPEARANCES:

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L. CECCHETTO)	General and Solicitor General
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	and Coroner's Office)
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	Nurses' Association of Ontario
	and 35 Registered Nurses at
	The Hospital for Sick Children

(Cont'd)



APPEARANCES: (Continued)

D. BROWN	Counsel for Susan Nelles - Nurse
G.R. STRATHY) E. FORSTER)	Counsel for Phyllis Trayner - Nurse
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W.W. TOBIAS	Counsel for Mr. & Mrs. Hines (parents of deceased child Jordan Hines)
J. SHINEHOFT	Counsel for Lorie Pacsai and Kevin Garnet (parents of deceased child Kevin Pacsai)



I N D E X o f W I T N E S S E S

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I N D E X o f E X H I B I T S

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220	Letter dated October 22, 1983 - Attention: The Honourable Mr. Justice Samuel Grange from John A. Olah.	2249
221	Photocopy of pages 158 and 159 of the virology book.	2297



---Upon commencing at 10:00 a.m.

THE COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Thank you, sir.

DR. STEPHEN PAUL SPIELBERG, Resumed

DIRECT EXAMINATION BY MR. LAMEK: (Continued)

Q. Dr. Spielberg, at the end of the day yesterday we were talking about Justin Cook. I want to go back to a couple of points about that child.

A. Sure.


Q. We spoke yesterday, and you gave it as your view that it was unlikely that the Cook blood concentrations of digoxin represented a steady state of distribution. Did I understand you correctly?

A. We can't tell for sure.

Q. Well, I know we can't but you said it was unlikely, did you not?

A. It would appear in a general sense that even with the significant amounts present in tissue that this still would probably not represent necessarily a steady state. = YES.

Q. All right. And indeed if we were to suggest that the 70 odd nanograms per millilitre of blood, in the blood did represent a



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1
2 steady state, it is unlikely is it not that the baby
3 would have died before reaching that full distribution
4 state?

5 A. I think particularly in this
6 child's clinical circumstances, yes.

7 Q. Yes.

8 A. If the heart had been normal
9 it would be very difficult to say under these
10 circumstances with the nature of the heart disease,
11 at least as I understand it, and again, I am not a
12 cardiologist.

13 Q. Yes.

14 A. That digoxin would potentially
15 be more toxic in a baby with a heart like this than,
16 say, a child with a normal heart.

17 Q. Now, have you read the reports
18 of the Centre of Forensic Sciences reporting the
19 results of the digoxin assays done there?

20 A. Yes, I have had a chance to
21 at least review them quickly.

22 Q. Do you have a copy of them
23 available to you?

24 A. I believe so. This is
25 Mr. Cimbura's report?

Q. That's right.



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2

A. Yes.

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Q. All right. I am interested in

4

Exhibit 95A, Mr. Commissioner. The first report
which is dated January 11th, 1982.

5

6

Now, could you turn to page 4 of that
report with me please, Dr. Spielberg.

7

8

A. Yes.

9

Q. At the top of the page

10

Mr. Cimbura continues certain notes that he had
added to the report of the levels recorded in the
various samples from Justin Cook.

11

12

A. Yes.

13

Q. Note No. 3 reads:

14

"The concentration of digoxin in the
heart muscle..."

15

and that was the fresh, as you will remember.

16

A. Yes.

17

Q. "...is above the range of

18

values found (literature reports and

19

research at the Centre) in persons on

20

digoxin therapy (49 to 975 nanograms

21

per gram in the ventricular muscle of
infants)..."

22

A. Yes.

23

Q. "...and is within the range

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"of concentrations reported in cases
of fatal poisoning (108 to 1240 nanograms
per gram)."

A. Yes.

Q. Now, you may not be familiar
with the research that Mr. Cimbura had done at the
Centre of Forensic Sciences but would you agree with
his proposition that the literature does indeed
disclose, or did indeed at that time disclose the
kind of ranges that he reports?

A. These are rough ranges with
a variety of different clinical situations.

Q. Yes, I understand.

A. None of them, as far as I am
aware, acute administration in an infant with a
very short period of time of distribution into
tissues. The piece of information that we are
lacking in essence is information on acute entry,
and by that I mean very rapid periods of time. We
searched very hard to see if we could find some
information on that specific issue because here most
of the cardiac concentrations in fatal poisonings
refer to the majority who are adults where we know
that levels in general are less. There are some
data in children and, in fact, we have some additional



1
2 data that has been accrued over time.

3 The gap that we are working with is,
4 what happens in the situation of a child like this
5 given what we have to accept as a large overdose
6 even if we are talking about a single vial of adult
7 digoxin. This still is a very large overdose
8 situation. Again, I don't mean in the least to
9 trivialize the quantities of digoxin that represents
10 for this child.

11 What we are lacking is information
12 on what happens when a child is given a dose like
13 this, perhaps 100 micrograms per kilogram - it is
14 a very large amount of digoxin - in the acute phase
15 because we don't really understand both specific and
16 non-specific binding in that acute phase distribution.
17 We just lack that information. Thus, if I have to
18 say, you know, is 975 the highest one can get in a
19 heart ---

20 Q. I'm not asking you that,
21 Dr. Spielberg.

22 A. Yes.

23 Q. I wasn't asking you that.
24 Will you please focus on my question which was this.

25 A. I am, sir.

Q. Which was this.



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A. I'm trying to give you an
answer.

4

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Q. I asked you whether you
agreed that as of January of 1982 the numbers reported
by Mr. Cimbura in Note No. 3 represent fairly those
recorded in the literature?

8

A. Yes.

9

10

Q. Now, you may tell me if you
will that the literature doesn't disclose a case
that exactly parallels the Cook case.

11

A. Yes.

12

13

Q. But with respect, my question
was a fairly simple one, was it not?

14

A. With respect to the literature
published values, that is correct.

15

16

17

18

Q. Thank you. I understand from
what you have said that your review of the literature
is that that does not disclose a situation that
exactly parallels that of Cook.

19

20

A. We tried to find such a
case and it is very hard and unfortunately we do not
have that information.

21

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Q. And similarly with respect
to Note No. 4 in which he records what the literature
discloses as to the concentrations of digoxin in



1
2 lung both as to persons on digoxin therapy and as to
3 cases of fatal poisoning. Do you agree, again,
4 subject perhaps to the reservations that there is
5 no parallel case to Cook, do you agree that as at
6 that time that was the sort of range disclosed by the
7 literature?

8 A. Yes. !

9 Q. Now, recognizing that
10 reservation on the literature, and by all means let's
11 come back to that, but recognizing that reservation
12 that you have expressed, it appears does it not
13 that the concentration recorded in the fresh heart
14 muscle of Justin Cook was very deeply into the
15 range of recorded levels in cases of fatal poisoning.

16 A. It is certainly very hard ^{high}
17 and certainly well within certainly the very upper
18 limits of therapeutic and into the toxic for, indeed,
19 we believe that he received a toxic dose.

20 Q. Yes. And indeed beyond the
21 then recorded upper limit of the therapeutic range
22 of concentrations?

23 A. Yes.

24 Q. And similarly with the lung
25 concentrations?

A. Yes.



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Q. And therefore may I have it that even at that point in the distribution curve which you posited yesterday as being the most likely scenario, the concentration in Cook's heart was already at a range which is apparently, in the literature, recognized as representing fatal poisoning?

A. Yes.

Q. Now, could you do a calculation for me, Dr. Spielberg, you are good at those. You have shown us what the measure of unbinding - what measure of unbinding might be necessary to increase serum level, I think in your chart by almost 39 nanograms and then again almost by 100 nanograms per millilitre, can you work back the other way?

A. It is hard but it is conceivable.

Q. All right.

A. But let's see if we can do it.

Q. All right. If the level in the blood of Cook represents something less than complete distribution.

A. Yes.

Q. Is it possible to say by how much or by what per cent the digoxin bound to tissue in Cook would increase while the serum level went



1
2 down to any number of your choosing. It would
3 continue to distribute on the hypothesis you were
4 putting to us yesterday, would it not?

5 A. The thing that we don't have,
6 the piece of information that we would need would be
7 the site at which the digoxin was initially injected,
8 the rapidity of uptake in the different organs during
9 that acute distribution phase and that information
10 too, which we had also looked for in the literature
11 is also unavailable. For example, if the relative
12 affinity of, say, cardiac ATPase were greater than
13 muscle so that during this acute distribution phase
14 accumulation in the heart occurred quickly and
15 accumulation in muscle, the mass of which is much
16 greater accumulated more slowly.

17 Q. Yes.

18 A. We really couldn't interpret
19 it. Now, with the situation with Justin Cook, again,
20 we are dealing with a huge amount of digoxin no matter
21 how we look at it, okay, regardless of how it got
22 there or whatever. Even a single vial becomes a
23 tremendous quantity of digoxin.

24 Now, let's say that half of it got in,
25 okay, and half of it distributed completely. This
will be, say, a 30 minute half life, okay, on the



1
2 average. This will be the equivalent of 50 micrograms
3 per kilogram distributing into that child.

4 Q. Okay.

5 A. This is still above a
6 therapeutic loading dose. Okay, so, we are still
7 talking about a toxic concentration distributing into
8 the body in a period of 30 minutes. To that extent,
9 since we know that patients who are on therapeutic
10 doses of digoxin can have levels in the 8 and 9 hundreds,
11 to that very limited extent we might be able to guess
12 that if half that amount of digoxin got in, let's
13 say he received 500 micrograms total, one vial, half
14 of that distributed into tissues, I would not be
15 surprised, for example, to find levels consistent
16 with children who were fully digitalized or a little
17 bit more, which could be as high as 900 or 1,000 or
18 1100.
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Now, that is a very crude
guesstimate: maybe 30 minutes, maybe more.
Again, the piece of information we are lacking
is just how the time dependents is in that very
brief distribution period. But I think if we
had to make a guess ---

Q. Well, I do not ask you to
guess if you do not have a reasonable measure of
confidence in it.

A. Yes, I think as far as we
can take it is to say that if the child indeed
received a full vial of adult digoxin that half
of that vial is more than a therapeutic dose.

Q. Yes.

A. And as such, if half of that
went into his tissues, in other words, that half
already was in his tissues and had distributed
with a half life of 20 minutes to 60 minutes, the
range we were talking about, I would not be
surprised that his tissues contained that much.

Now, I realize that is a big
range and I think that is about as close as we
could ever hope to come.

Q. Okay. You cannot do the
calculation back the other way. There are pieces



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of information that are missing.

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May I have this at least, that on the basis of the assumption that you made, that the blood and tissue levels represented some point along the -- still in the alpha phase of distribution, that had distribution continued, the probability is that both the heart and the lung tissues would have achieved greater concentrations?

A. Again, I do not know that because ---

Q. I know you do not know it, but is it probable?

A. I cannot even give you a straight answer because I do not know if those tissues were saturated and other tissues --

Q. You do not even know if there is saturation?

A. -- and other tissues were not saturated. For example, if we had muscle and a whole phase of other organs available, then we could sort of make a guesstimate back of the total body digoxin, in other words, how much was in muscle, how much was in liver, how much was in heart, how much was in lung, how much was in



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skin. From all of those, then we could make a guesstimate, and even at that it would still be a guesstimate back, whether we had reached a maximal amount in tissue and whether the level might have stayed up in serum or whether it would have continued to decline over a very long period of time as again excretion occurred.

Q. Let us pause. In the first place, Doctor, I thought you told us yesterday that you do not even know if there is saturation in tissue. That is probable but you do not know that?

A. We do not know about that.

Q. Not knowing that, you cannot say whether it is likely that a saturation point had been reached, there may not be one?

A. There might not and there might, exactly.

Q. Second, does not the very hypothesis that you made yesterday necessarily assume that further distribution to tissue will occur?

A. To some tissues ---

Q. Otherwise 78 is steady state, is it not?



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A. Presumably there would be some further distribution, yes. But again, the piece of information we are lacking is that we do not have the other tissues to know that.

Q. All right. Now, you, yesterday, gave us your views, your opinions as to the minimum and maximum doses to achieve the serum levels recorded in Justin Cook. I think the level recorded at the Hospital was 72, not the 78 you talked about, but that may not be material.

A. It is a small difference, yes.

Q. Yes. And equally, I think the serum level at the CFS was 69?

A. Sixty-nine, yes.

Q. Now, you did not yesterday, because frankly you were discouraged from doing so, go through the calculation which produced the levels, the doses that you were suggesting. Now, I wonder if, please, you could tell me what the assumptions and figures were that you used in arriving at those conclusions?

A. Surely. First, what we need -- can I use the blackboard?



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Q. Yes, of course.

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A. The first piece of

information we need is a level, obviously, and
as such, we can take 70 nanograms per ml. Can
we use that as a ---

Q. I am content, yes.

A. You are comfortable.

Seventy nanograms per ml. Now, the issue, then,
is that we are sampling from serum, presumably,
although there is some question actually in this
case whether the readings are whole blood or
serum. There is one serum value which actually
is half that that Mr. Cimbura recorded at 49,
so the whole blood, because red cells
particularly in infants have a high concentration,
may give you a different reading than serum.

Q. Do you know what the
Hospital's practice is?

A. We typically, in therapeutic
monitoring, use serum. Forensically, some people
will use whole blood and other people will use
serum. Most of the readings I believe that Mr.
Cimbura has on there are whole blood. There is
one serum value which is in the forties -- 46,
yellowish fluid reported to be serum, 46. So again,



1
2 we are talking ranges here, albeit still large
3 numbers and of major concern.

4 Q. Yes.

5 A. Okay. Now, we are saying
6 that this child is approximately five kilos. I
7 think he was five point --

8 Q. Three six.

9 A. -- three kilos. Can we use
10 five kilograms? It will make it a little bit
11 easier.

12 The question that we are then
13 asking is in what time-related manners can
14 digoxin distribute in various different what we
15 call pharmacologically compartments within the
16 body. Again, they are not anatomic compartments
17 necessarily; they are pharmacologic constructs.

18 If it is injected immediately into
19 the bloodstream, okay, and presumably no
20 distribution or it is just distributed within
21 blood and has not left serum, including no binding
22 to red cells or what have you, then we are
23 talking about approximately, and it is going to
24 vary from child to child and adult to adult, and
25 I arbitrarily used approximately 40 ml of serum
per kilogram of body weight. So that if we only



1
2 distributed in that small amount of serum, then
3 we are talking about that 70 -- we are talking
4 about how much total volume. Well, it will be
5 five kilograms of body weight times 40 ml of
6 serum, which comes out, then, to approximately
7 200 millilitres.

8 Now, the question, then, is how
9 much digoxin would be present in that entire
10 amount. We have said there are about 70 nanograms
11 per millilitre. Now we are saying that that is
12 dissolved only in serum and we are saying that
13 maybe there is 200 ml of serum. Then we have to
14 multiply 70 nanograms times 200 millilitres. This
15 is in nanograms now. To convert this into
16 administratable units, okay, which will be
17 micrograms, which is the usual way we would think
18 about these things, we have to move the decimal
19 point three places since a nanogram is one
20 thousandth of a microgram, and we come up with
21 about 14 micrograms.

22 Now, we already stated that that
23 is really rather unlikely under these
24 circumstances.

25 Q. Yes.

A. Now, when we are talking



1
2 about central volumes of distribution, the
3 volumes of distribution generally give a range,
4 and here I have to again state we are dealing
5 with big, broad ranges. In very young children
6 premature infants, we are talking about a litre
7 per kilogram; in older children we are talking
8 often in the range of 0.5 litres per kilogram
9 with a lot of variation on either side.

10 So again, I want to caution that
11 the calculations are, at best, gross and rough.
12 Under these circumstances, let us take initially
13 one litre per kilogram and then we will take a
14 half litre per kilogram, now we are talking about
15 this same concentration arising from digoxin
16 being dissolved in a much larger volume of fluid.

17 In the case of one litre per
18 kilogram, the child is five kilograms, then the
19 volume becomes five litres. If we are talking
20 about a half of a litre, then we are talking
21 about 2.5 litres.

22 Now, the question again is what
23 concentration of digoxin would have to be
24 administered, assuming it dissolves in this volume
25 to produce this concentration. Now, in order
to do that, we are going to have to do a slight

*Arbitrarily
conservative -
Kaufman. 1.74 kg.*



1
2 conversion up here because we are no longer
3 talking about millilitres, we are talking about
4 litres. Now, 70 nanograms per millilitre
5 converts to 70 micrograms per litre. This is
6 again moving the decimal point three places here
7 and three places here.

8 So now we have a concentration of
9 70 micrograms per litre and a volume of five
10 litres. So five times 70 comes out 350
11 micrograms.

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2 Here we multiply blood and hopefully it should be
3 approximately half that, which would be about 175
4 micrograms, now again we are talking very broad
5 ranges, it could have been more, it could have been
6 less.

7 Now, when we are talking of 15 litres
8 per kilogram - now again this is under the assumption
9 that that volume of digoxin could indeed be
10 distributed throughout the body, and again frankly
11 we just don't have the data on that, if the child
12 is given an acute dose that high, and again what kind
13 of tissue levels are going to be achieved and if
14 it can completely distribute. Let us assume it can
15 be distributed for indeed that is what some of the
16 initial testimony was related to. Then we have to
17 multiply - I am going to have to use my calculator,
18 350 times 15, so 350 times 15 comes out approximately
19 5.3, and again I wouldn't really take the 3 because
20 we are really doing crude examples, this would be
21 5 milligrams and this would be about $2\frac{1}{2}$ milligrams.

22 So again the absolute constraints you
23 can put on things would be this minimum which we
24 said really is unlikely I think given the child's
25 tissue levels. Something in between, and again we
really can't say because we are lacking information



1C2

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2
3 as to time, and with the lack of information about
4 time all we can do is guess. So we will use this
5 initially, but in fact if it had been half distributed
6 in- this might have been 350, had the volume for
7 distribution been this, or this could then be 700
8 and the volume being distributed, so it becomes very
9 difficult, because we are walking along a continuously
10 changing curve not knowing the route of administration,
11 and not knowing the time of administration, and not
12 knowing the amount of administration.

13 In terms of the tissue level accrual
14 again all we can say is yes, the concentrations are
15 consistent with a large dose of digoxin having been
16 administered.

17 If we had a child who was completely
18 stable, who had been digitalized and was entirely
19 stable and died in a car accident say, for example,
20 and we got back a level of 1100, we would say that
21 is probably also consistent with therapeutic, yet we
22 know in this situation this child had a very high
23 blood level and a very high tissue level. The only
24 reasonable postulate is he received a large dose of
25 digoxin.

Beyond those constraints I think one
has to be very cautious in making any further



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3 interpretations. It could again have occurred
4 among all of these various medicines that he was
5 receiving prior to his arrest. It is conceivable
6 that it could have been administered after arrest.
7 I think there is no hard scientific way given the
8 vast variation from patient to patient and the
9 vast kinds of differences that we are talking about
10 here to carry it very much further unfortunately.
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Spielberg, dr.ex.
(Lamek)

C/DM/ak

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Q. Thank you for that, Doctor.

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You say we don't know the route of administration,
4 doesn't your model rather assume a single IV bolus
5 administration?

6

A. Oh yes, I meant by route size.

7

Q. Route size?

8

A. Yes, in terms of the potential

9

for example of intracardiac which again might change
our understanding of the rate of accumulation of

10

heart/lung versus the rest of the body. Again how

11

much influence that would have I honestly don't

12

know.

13

Q. Did I understand you right

14

yesterday, Doctor, to be saying that the further one
progresses along the alpha phase of distribution ~~that~~ ^{with}

15

this exercise of estimating the dose necessary to

16

produce the known result, the further one progresses

17

towards steady state the larger the dose which one

18

would calculate to produce that level?

19

A. Yes, I think that is basically

20

fair, sure. Because basically what would be happening

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under those circumstances you are talking about larger

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and larger volumes that the drug would have to be

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absorbed.

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Q. Yes. You also told me

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yesterday afternoon at the very end of the day that had the drug been administered, for example at I think the time was 4:32, in the course of the resuscitation effort on the first occasion of intracardiac injection of ^athe drug, that you thought it could, in the space of the following 24 minutes, achieve the degree of distribution necessary to show up the concentration that we have in the heart muscle.

A. Conceivably, yes.

Q. That is conceivable, it is not likely though is it, Doctor?

A. I can't put a probability on it, again because of the lack of information and the lack of knowledge whether the drug was placed directly in the heart by that route. It is something that might be approachable experimentally, so that we might be able to at some point in the future, or someone might be able to get that answer. I think it has to be accepted as a possibility and how probable it is, well again we are talking about perhaps let's use 500 micrograms under those circumstances, and if half of it got in during that half life in that child even in the absence of adequate circulation it certainly must be admitted during resuscitation, there is some circulation



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going on but it is not optimal.

3

Q. Yes.

4

A. It still has to be at least
considered a possibility.

6

Q. A possibility?

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A. Yes.

8

Q. I take it though you would
acknowledge equally the possibility that the drug
was administered rather more than half an hour before
death?

10

11

A. Yes, I think that has to be
accepted as a possibility. Again we know that many
medications were being given to this child in the
time prior to his arrest. This opens the opportunity
again for the conceivable error being made during
the administration of all these various different
drugs. Or obviously the other possibility which is
intentional administration, which again in no way
can I rule out as a pharmacologist.

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Q. No, of course not. But if
in fact the drug is given more than half an hour
before death, could it be as much as an hour before
death, an hour and half before death?

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A. Again I think we would be
really, really guessing.

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Q. Are those numbers as possible
at half an hour?

A. If - and again if I had to
take my "best guess" I would put the constraints
reasonably close to the time of death, again because
of the baby's condition and the probability of
events occurring, i.e. a fatal type of event occurring
as the digoxin began to accumulate within the heart,
if that was indeed the proximal cause.

So I think the further one goes out
prior to the actual events at shortly after 4:00 in
the morning, I don't remember, 4:10, or whenever the
actual arrest was called, 4:20 in the morning, it
really becomes harder and harder to think about longer
and longer times.

Q. I take it ---

A. Again with the variability
we see and the tremendous differences in the onset
of toxicity I think it would be foolish to try to
say anything further in terms of time.

Q. All right.

A. The closer becomes more
probable, the further becomes less probable.

Q. I take it what you have to
do, you have to balance two things, the probability

like an
arrest?



2C5

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of toxicity manifesting itself at a relatively early point after administration in this child?

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A. That is right.

5

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Q. With the established accumulation of the drug which had already distributed to the tissue.

7

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A. Yes.

9

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Q. Somehow those two have to be reconciled have they not?

11

12

A. Yes, because we already have - again assuming it is bound to the receptor and we can't argue one way or the other, but probably it is.

13

14

Q. Yes.

15

A. Assuming that that is the case then we have to cope with the fact that there is a lot already in the heart.

16

17

Q. And that doesn't happen in the flash of an eye I take it?

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A. Again presumably it does not. You know, one of the things that we tried to find in the literature so hard and that we don't know, is whether - and again that is why I can't give you better timing on it, and I don't think anyone can sadly, is that we don't know what happens when a very, very large amount is given, and again this is a very,



2C6

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3 very larger amount, it is at least four times what
4 one would ever give as a single dose. You know,
5 when we are talking half a milligram, since we would
6 rarely if ever give more than 20 micrograms per
7 kilogram and we are talking in the range of almost
8 100 micrograms. What we don't really know is what
9 that alpha phase looks like in that kind of huge
10 overdose. It might be more rapid, it might be
11 slower, and under those circumstances again I think
12 pharmacologically we would be foolish trying to give
13 you any tighter kinds of time constraints.
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2 It frustrates us, too, because
3 if we could give you tighter time constraints
4 then we could fit it better with the clinical
5 course.

6 Q. Yes.

7 A. And then we can say with a
8 degree of more assurance what is more or what is
9 less likely and I am afraid I can't.

10 Q. Well, I understand the difficulty,
11 Dr. Spielberg. Can we go this far, that the greater
12 the interval between death and administration the
13 larger the dose that you would calculate in order
14 to arrive at the most likely scenario, is it not?

15 A. Yes. Again, just looking
16 at the curves that we presented, assuming the
17 distribution is going on with that sort of time
18 course that is a valid assumption, yes, sir.

19 THE COMMISSIONER: Could I have that
20 again, please?

21 MR. LAMEK: Yes. The greater the
22 interval between administration and death and,
23 therefore, the greater period for distribution
24 out of blood and into tissue --

25 THE COMMISSIONER: You mean the
interval back?

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THE WITNESS: Yes.

MR. LAMEK: Yes.

THE COMMISSIONER: Back from death.

THE WITNESS: Right. So, you know, for instance, if we would be talking --

MR. LAMEK: Wait, let the Commissioner be sure that he has it first.

THE WITNESS: Okay.

THE COMMISSIONER: Well, no, I was just delighted when we got an answer, that's all. The greater interval back from death to the time of administration, is that right?

MR. LAMEK: Yes.

THE COMMISSIONER: Then what happens?

MR. LAMEK: The higher the dose that Dr. Spielberg would calculate to produce the level measured in the blood.

THE COMMISSIONER: Yes, all right, that sounds reasonable.

MR. LAMEK: Q. Now, if I have understood your calculation this morning, Dr. Spielberg, and forgive me I am looking at it in a rather funny angle.

A. Yes, sure.

Q. Do I understand that your



1
2 calculation came out at about 350 micrograms, given the
3 assumptions that you have made in there?

4 A. This was somewhere in, say, the
5 range from 175 to 500 to be, you know, reasonably
6 fair. That would assume that the drug now ^{is} ~~has~~ less ⁱⁿ
7 serum and has entered at least the central volume
8 of distribution and then is somewhere along that
9 curve, distributing into tissue, how far we do not
know.

10 Q. Okay. But how far is important,
11 is it not, because the further it progresses distribut-
12 ing into tissue the greater your calculated dose is
13 going to be. I am considering for a moment the
14 suggestion that you were making yesterday of perhaps
15 accidental administration. Will you agree with me,
16 Doctor, that the possibility of accidental administra-
17 tion becomes less feasible if you have to assume a
dose greater than one adult vial?

18 A. Yes. As soon as it requires, for
19 example, the time and the effort dependent on open-
20 ing multiple vials ---

21 Q. Even two.

22 A. Again conceivably, unless you are
23 given two medicines and make two medication errors.

24 Q. Yes.
25



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A. But again that probability
certainly begins declining.

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Q. And, therefore, if in fact this
administration occurred at ^{a time} ~~sufficient~~ ^{by} removed
from death to produce a new calculation - a dose
greater than one adult vial - then I would take it
the suggestion of accidental administration becomes
a little less plausible, does it?

9

10

11

A. Any time we have to postulate
opening multiple vials accident becomes less
plausible, yes.

12

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Q. Now, we know that you have told
us the range of calculation you have made reaches the
upper limit of one vial, the 500 micrograms and,
therefore, not much in the way of variation of that
calculation would produce a range that extended
beyond 500 micrograms, I take it.

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A. Sure. In other words, what we
have to view is the possibility. Again, the lower
range doesn't make sense. The range from 175, which is
a fraction of one vial, then has to be considered all
the way up to what I think is a remote possibility;
in other words, that we get up all the way to the
15, 20 vial theory, but we have to consider every-
thing within that range.



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Q. Yes. And although I recognize

3

that --

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THE COMMISSIONER: I'm sorry, are we
talking about -- how many vials did you say?

5

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THE WITNESS: Well, when we are down
to 5 milligrams we are talking ten adult vials.

7

8

MR. LAMEK: Q. The notional
maximum?

9

10

A. Yes, ten adult vials or perhaps
one hundred pediatric vials.

11

Q. Yes.

12

THE COMMISSIONER: I think you got to
5.8 yesterday.

13

14

THE WITNESS: Yes, right.

15

THE COMMISSIONER: Which would be
12 and 120.

16

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THE WITNESS: Right, that's correct.
That's correct.

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MR. LAMEK: And I take it, Doctor, that
you cannot tell us, and I am certainly not critical,
you cannot tell us with any assurance what point
along that alpha phase curve had been reached at the
time of Justin Cook's death.

22

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A. We can't with any degree of
assurance, not knowing the amounts and not knowing



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the time.

3

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Q. But the point along the alpha phase curve determines, does it not, the volume of distribution that you plug into your calculation?

6

A. Yes.

7

8

Q. And the further along the curve the higher the volume of distribution that you are going to plug in?

9

10

A. Yes. Again, assuming distribution is going on, absolutely correct.

11

Q. Yes.

12

A. Yes.

13

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15

Q. And that gets multiplied through the calculation to produce obviously, as we have said, an increasingly higher solution at the bottom of the calculation?

16

A. Yes.

17

18

Q. Can we turn to the case, please, of Allana Miller.

19

A. Yes.

20

Q. I think the chart is right there beside you.

21

A. Oh, fine, thank you.

22

23

Q. I'm sorry, just before we leave Justin Cook, can I put a couple of assumptions to you

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2 in the calculations? If, instead of a volume of
3 distribution of one litre per kilogram, which I under-
4 stand is the one you used here.

5 A. Right.

6 Q. One assumes a volume of distribu-
7 tion of 1.3 litres per kilogram, suggesting a little
8 further progression along the distribution phase,
9 would you regard that as a reasonable assumption to
10 make in doing this calculation?

11 A. I think in thinking about it we
12 have to consider every possibility, yes, exactly.

13 Q. Yes, you wouldn't reject that.
14 as a totally unreasonable assumption.

15 A. Not at all.

16 Q. In estimating the time interval
17 between the dose and death, do you consider it
18 reasonable or unreasonable to estimate a period of
19 one to two hours?

20 A. I cannot rule it out. I think
21 it becomes again less likely.

22 Q. All right.

23 A. I think it is possible and I
24 think we would be foolish again to try to really put
25 any time constraints on it.

Q. Well, may I have it, it is not

Kaufmann's
assumed
central v.D.

11



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an outrageous assumption but it is one that you
would have a bit of a misgiving about.

4

A. I would feel more comfortable.

5

The closer I think given the variability and given
everything that we know about the complexity it has
to be considered possible.

7

D-2

Q. Now, I referred you yesterday

8

to what Dr. Rowe had said about Justin Cook. I think
I should also tell you what he said about other
children, including Allana Miller.

10

11

A. Yes.

12

Q. At Volume 18, Mr. Commissioner,

13

Page 3275 I asked of Dr. Rowe this question and
received from him this answer:

14

"Q. Doctor, of all the 36 deaths
that we have reviewed together over the
past three weeks, and I know that you
have said that after March, 1981 you
had to consider all of those deaths
as possibly having been caused by
digoxin intoxication. Let me ask you,
of the 36, which do you now regard as
most likely to have been caused by
digoxin intoxication?"

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And Dr. Rowe's answer was this:

24

"A. Well, I think that Cook

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2 unquestionably is one that I think that
3 had happened. I think it is possible
4 that a number of others that where the
5 evidence, and I use that knowing that I
6 am not an expert in that area, it seems
7 to me from the information that I have,
8 at least subject to further discussion
9 and debate by people who are experts
in their fields..."

10 and he meant you,

11 "...I would put about 6 others in
12 that category.

13 Q. You tell us which 6, will you,
14 Doctor?

15 A. Miller is one, Pacsai is another,
16 Inwood is another, Hines is another and
Estrella is another."

17 And then he added Velasquez. It is clear that he
18 was talking about some other drug involvement with
19 Velasquez.

20 A. Yes.

21 THE COMMISSIONER: And he also added
the next day ---

22 MR. LAMEK: He added ^{De}~~Bou~~langer sub-
23 sequently.
24
25



1
2 THE COMMISSIONER: And Lombardo.

3 MR. LAMEK: And subsequently Lombardo,
4 yes. But having now read that to you once I won't
5 read it to you again each time we come to these
6 children. Each of the children whose charts you
7 reviewed and about whom we are going to talk were
8 regarded, I think fairly by Dr. Rowe, subject
9 to the pharmacologic opinion and the resolution
10 of any pharmacological disputes, were considered by
11 him to be most likely to have died as a result of
12 digoxin intoxication.

13 A. And I would certainly share the
14 concern.

15 Q. Yes. Now, I take it, Dr.
16 Spielberg, that with Allana Miller ~~do~~ we have a
17 picture that is rather different from that of Justin
18 Cook.

19 A. Yes.

20 Q. We have here a child who had
21 been on digoxin therapy.

22 A. Yes.

23 Q. And certainly she seems to have
24 had high post-mortem blood levels, 78 recorded at
25 the hospital, 69 at the Centre.

A. Yes.



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Q. There are no fresh tissue
samples.

4

A. That's correct.

5

6

Q. And there are low levels
recorded in fixed heart and lung.

7

A. Yes, I believe the lowest in Mr.
Cimbura's series.

8

9

10

Q. Yes. Now, I take it that in
the case of Miller's, dealing only for the moment
with the digoxin measurements.

11

A. Yes.

12

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Q. That you would regard the post-
mortem blood level as the only significant digoxin
information.

14

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A. Well, I think there was one pre-
mortem, wasn't there? Yes, there was one level two
days prior.

17

Q. Yes.

18

19

A. Which was 0.6. So, we have
to take that into consideration as well.

20

Q. Yes, you are quite right.

21

A. She had low therapeutic levels
at least two days prior to her death.

22

23

Q. Yes. And then a post-mortem
level at autopsy of between 69 and 78.

24

25



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2 A. Now, I think again sadly the
3 postmortem fixed tissue level, given the tremendous
4 variability and including in Mr.Cimbura's subsequent
5 studies, it becomes impossible to predict anything
6 of that, so I would think ---

7 Q. He would not disagree with
8 that.

9 A. In a realistic sense I am afraid
10 that we have but one level to deal with.

11 Q. All right. Now, as far as
12 digoxin administration to this child is concerned,
13 at Page 29 of the chart which you have, Dr.
14 Spielberg, it appears that on March 19th, 1981.

15 A. Yes.

16 Q. Dr. Kantak wrote orders first for
17 a digoxin level and, second, to hold digoxin for now.

18 A. Yes.

19 Q. At Page 43 of the chart it
20 appears that Dr. Kobayashi on March 20th at what I
21 can only believe is 1500 hours.

22 A. Yes.

23 Q. I wouldn't think it was 75.

24 A. Yes.

25 Q. At three o'clock in the afternoon
on the 20th.



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A. Right.

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Q. Apparently ordered the resumption
of digoxin at a maintenance dose of .032 milligrams
orally twice a day.

5

6

A. Yes, that's correct.

7

8

Q. Right. And then at 2:30 on the
morning of March 21st Dr. Soulioti ordered the
digoxin be held again.

9

10

11

12

A. Yes.

Q. All right. And that in the
immediate period prior to her death seems to have
been the pattern.

13

14

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A. Yes, in terms of administration
of the medication ordered on the 20th, I see one
nursing note indicating that one oral dose had
been administered at 2100.

16

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Q. That's right, yes.

A. On the 20th.

Q. Yes.

A. So that we know that one dose
had been administered at that time.

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Q. The orders in short seem to
have been carried out.

22

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24

25

A. Yes. There seems to be agree-
ment between order and record of administration.



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2 Q. Yes. Now, at Page 42 in the
3 progress notes much of the page is taken up by a
4 note by Nurse Nelles and the second half of that
5 note, beginning just half way down the page.

6 A. Right.

7 Q. Reads:

8 "At approximately 1:45 baby's apex
9 was noted to be 54 and very irregular."

10 A. Yes.

11 Q. "Blood pressure down to 98 over
12 pulse."

13 A. Yes.

14 Q. "Child was stimulated and apex
15 came up to 70. This happened three
16 to four times."

17 A. Yes.

18 Q. "And then the child began to
19 gag and vomit. Large amounts of very
20 thick clear mucous. She was suctioned
21 for further amounts of this mucous."

22 And the footnote, the asterisk:

23 "Respiration became quite laboured,
24 substernal and intercostal indrawing
25 very noticeable."

Reverting to the note:



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And then:

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"Dr. Soulioti came at 2:40. At approximately 2:45 baby began to seizure and i.e. became very rigid and extended legs and arms. On auscultation there was no heart rate, so, CPR was initiated. Code 25 called."

"See the physician's note for resuscitation effort."

A. Resuscitation, yes.

Q. "Baby pronounced dead at 3:27 in the morning."



/BN/ak

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3 Now, in light of Dr. Soulioti's order
4 at 2:30 in the morning of the 21st to hold digoxin,
5 I take it you will agree with me that the likelihood
6 is that it was when he was called to that baby in
7 the middle of the night and saw him that he wrote
8 that order?

9 A. Presumably, yes.

10 Q. And a reasonable inference, I
11 would suggest to you, can be that he suspected the
12 possibility of some toxicity?

13 A. Yes, and you know, certainly
14 here was a baby who had bradycardia, and again, we
15 said that two possibilities exist: one, the baby's
16 clinical disease, and two, the possibility of digoxin
17 toxicity either from an excessive amount or because
18 everything else was out of balance. It seems like
19 a very reasonable clinical response.

20 Q. It is a prudent move to make
21 in that situation?

22 A. Certainly, to hold the level
23 which was not due for another many hours at that
24 point, but to at least consider holding the next
25 dose until you had a level and then proceed.

Q. Because the record discloses
bradycardia and irregularity, which is not necessarily



E2

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the same thing as bradycardia, is it?

3

A. That is correct.

4

Q. And some vomiting?

5

A. That is correct.

6

Q. Again, a very non-specific

7

symptom but nonetheless a known symptom of digoxin toxicity?

8

A. Certainly.

9

Q. Now, Doctor, I certainly

10

would like to hear from you what, if anything, you

11

regard of importance in this chart in coming to your

12

expert medical and pharmacological opinion about

13

this child, but can you take me to the bottom line

14

first. Do you have an opinion as a clinical

15

pharmacologist and indeed as a physician as to

16

whether digoxin toxicity played a part in this child's death?

17

A. I think it is indeed possible.

18

I am concerned that it did, as Dr. Rowe was concerned that it did.

19

20

There are several reasons one has to

21

be concerned, the primary one being that we have an

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extraordinarily high postmortem blood level. In

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order to deal with the issue of how confident we

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are that it contributed to the death, again, we have

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to deal with how the level got to be that high, and there are several things we will have to touch on. One is administration which has to be considered a possibility, indeed, a probability that the child received a dose of digoxin which produced that ---

Q. An unprescribed dose?

A. An unprescribed dose of digoxin which produced that kind of level, or that the level may have some artefacts or have been "created through a series of circumstances unrelated to administration".

Q. Certainly.

A. And in order to do that, we first have to look at the patient clinically and then we have to look at the post mortem and balance whether all those things off and decide/administration then becomes the most likely of the possibilities.

Q. Fine. Could you take us to that exercise, please?

A. Now, Allana Miller was a very sick little baby. I gather in the three months prior to her admission she had gained no weight and there was major concern that she was doing poorly and would need some sort of intervention, surgical or whatever, rather soon.



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There are some things we do not understand very well about what led to this particular admission. First, we are told that she had fallen several times and bruised herself. I do not know what role that played in any of it, but in any case, very soon thereafter she developed a fever and had a seizure. She was seen at St. Mary's Hospital, where at that time she had evidence of having had a seizure, was indeed febrile. The question at that time was raised of the possibility of sepsis, in other words, a systemic infection.

She also had an elevated blood urea nitrogen, which was recorded there as 46, suggesting that her kidneys or profusion of her kidneys at that point was not very good.

She then arrived at the Hospital for Sick Children. She was found to have an irregular, slow heart rate at admission. Her heart rate was 80, rhythm was described as junctional and irregular.

Now, recognizing that that rhythm corresponds to a digoxin level that at that time when it was taken was low therapeutic, so that we cannot attribute her irregularity in heart rate nor her bradycardia when she arrived at the Hospital to excessive digoxin.



E5

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She then proceeded to be put on anti-biotics, which was a very reasonable response in a child who was febrile. She then continued, during the 19th, to have heart rate varying from 70 to 108, had reddish eyes and green discharge from her eyes, all consistent with the possibility that she might have an infectious process going on, and had a large bloody stool, which had also been reported from St. Mary's. So we have a child here who had cardiac disease, who was febrile, who had had a seizure, who had a bloody stool, and at the time, her temperature actually was falling to 35.7, which suggests, again, hypothermia or decreased temperature in babies is often a terribly bad sign because it often means that they are quite acutely ill and no longer can maintain their body temperature.

Then we are told that she had a white count of 18,000 and a falling platelet count in the range of 89,000, again, all consistent with a terribly ill child, possibly infected, possibly not, going along again with bloody stools.

Now, I cannot tell you to what extent that disease process contributed to changes in digoxin because we never really learned what the disease process was. Even at autopsy we do not understand



E6

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2 why she was febrile, why she seized, nor why she had
3 blood in her stool. We do not have bacteriology
4 or virology reports to help us in that regard, so
5 I have nothing really to say in terms of digoxin
6 with respect to her illness except something may
7 have been going on; we cannot define it.

8 Then we come to an episode -- all during
9 this time, the chart records irregular heart rate,
10 bradycardia, junctional rhythms, continuous changes
11 in rate, and a very sick baby. Then, I gather, at
12 some time before 2:00, again, her heart rate is showing
13 even more irregularity. Can, again, we separate
14 that irregularity and slowing of heart compared to
15 the slowing of heart she had before. It is
16 certainly consistent with her clinical disease as
17 she progressed up to this point, so we cannot say
18 one way or another whether digoxin was playing a
19 role then.

20 Then at 2:40 lasix is given, and I
21 am concerned about this, and concerned for two
22 reasons: one, an intravenous medication was given
23 at 2:40, and second, at 2:45 the patient seizes and
24 goes into asystole. Her heart rate stops, so this
25 is an arrest, in fact, where the heart stopped. I
am concerned about that for several reasons: one is



E7

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2 the time course. We are talking about an intravenous
3 medication. We do not know where it was placed in
4 the line, whether it was high up in the line or low
5 down in the line, but an intravenous administration
6 of a medication that very shortly within a matter of
7 minutes led to a seizure and to an arrest.

8 Q. Was followed by a seizure?

9 A. Yes, excuse me, quite correct.
10 But a very tight temporal association.

11 Now, this could be completely coincidence.
12 In fact, the baby, from the description in the
13 previous period of time, seems to be getting worse,
14 maybe from her disease and perhaps from something
15 else. She seems to be getting worse and worse, but
16 then suddenly a drug is administered and a very
17 short time thereafter she becomes much worse. So I
18 am concerned about that administration. Lasix or
19 furosemide is a diuretic. What it normally does is
20 it helps the kidney to excrete water and salt, and
21 might be an appropriate response in a child, for
22 example, who is gagging and whose lungs were filling
23 with fluid. So that the order does not disturb me.
24 The request for lasix is not a problem.

25 However, when one orders lasix, which
is not normally present in the standard orders, in



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other words, this was not a standing order in the chart, give lasix every so many hours for such and such symptoms, one has to wonder could the lasix have contributed to this child's arrest. In other words, we are asking given the temporal association, could the drug have played a role in the child's arrest.

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I think this is reasonably unlikely for lasix. The toxicity of the drug usually is causing excess fluid loss, but that happens later. It does not happen instantly; it does not happen very rapidly. There is some evidence that lasix can in fact cause a decreased tone in large veins that lead to the heart. In other words, ordinarily the veins that fill the heart have a certain degree of muscle tone in them, and sometimes lasix, particularly acutely, can cause some relaxation of those what we call capacitance vessels, bringing blood back to the heart, and that could conceivably cause an acute change in blood pressure, but I do not think so. Therefore, I am very worried about that, the temporal sequence. What might have caused that, and here we get into conjecture and I have to offer you conjecture because we have to deal with the fact, number one, something happened rather quickly, and number two, there is the presence



E9

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2 of digoxin in this baby at the time of autopsy, and
3 one possibility which I think we have to consider
4 is that the baby did not receive lasix, but rather
5 that that dose might have been digoxin. It is a
6 possibility.

7 The two possible ways that that could
8 have occurred is that somebody intentionally gave
9 the baby a dose of digoxin. That has to be accepted
10 as a possibility. The other possibility is a
11 medication error, again confusing a vial of digoxin
12 and a vial of lasix. I cannot distinguish between
13 those two in terms of the way in which they would
14 have occurred.

15 In terms of how the drug ends up in
16 the baby, it is not the resident says, "I need
17 lasix" and suddenly a vial of lasix appears. It is
18 a complex process, and I again do not know what
19 happened. What has to occur is that somebody has
20 to provide a vial of the drug, somebody has to draw
21 the drug up. They might want to dilute it since the
22 volumes are very small. I do not know if they did,
23 which requires the drawing up of a second vial of
24 normal saline or appropriate diluent. Then the
25 syringe has to either be handed to somebody who
administers it, the resident or the resident himself



E10

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2 drew it up, and I do not know which, and the drug is
3 administered.

4 So to simply say lasix was given is a
5 complex process involving perhaps several people and
6 perhaps involving one person.

7 Now, we get to a problem. If this
8 was digoxin, from everything I have told you, should
9 the baby have arrested if he simply had a very high
10 level of digoxin? We said if it is not in the
11 tissues now, should that cause an arrest. We have
12 got a problem. Injectable digoxin is not injectable
13 digoxin alone. Injectable digoxin contains several
14 different compounds which we have to deal with
15 right now and which may or may not be tremendously
16 relevant to the issue and also to Justin Cook and
17 also to some of the other babies. Injectable digoxin
18 is 40 per cent propylene glycol. Propylene glycol
19 is a very safe medicine and it is used in the
20 pharmaceutical industry to suspend drugs that are
21 not soluble. Now, the reason the propylene glycol
22 is used is that it is generally rather safe. However,
23 there are certain circumstances where propylene
24 glycol is extremely toxic, and the problem is very
25 nicely exemplified, for example, by injectable
valium, which is used in seizures, and that is where



Spielberg, dr.ex.
(Lamek)

E11

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we have most of our experience with propylene glycol toxicity. We also have it with dilantin, which is an anti-convulscent, similarly suspended in propylene glycol. .

If a solution containing propylene glycol. is injected rapidly into a patient, too rapidly, a series of events can occur: cardiac arrhythmias, hypotension, loss of blood pressure, cardiac arrest, respiratory arrest and death. I believe that there is quite a good deal of literature with respect to the effect of over-rapid injection of valium and over-rapid injection of dilantin into patients causing arrhythmias, hypotension and death.



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This is an acute phenomena, it happens rapidly.

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It is also one of the reasons why large volumes

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of digoxin become less and less likely as

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probabilities, because basically babies would not

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be able to tolerate the kinds of propylene glycoll

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concentrations in many vials, or even in several

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vials.

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What are the consequences of this?

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The consequences of this and what concerns me as

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a pharmacologist, is that if either an error is

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made, or someone intentionally administers a

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significant vial or dose of digoxin as an

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intravenous push, in fact the baby might die of

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propylene glycol toxicity way before he ever died

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of toxicity from the drug itself, i.e. digoxin.

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Some distribution could still occur subsequently,

everything is time dependent and we don't know

the time.

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In honesty some of these

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considerations have only occurred to me within the

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last day re-reading the charts. I have missed the

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fact that this baby was given something

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intravenously within five minutes of asystole.

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I do not have full information on propylene glycoll

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doses and toxicity which might or might not be

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expected to do this. I have somebody in my laboratory now trying to dig out this information.

It may be important to think about. I think it is important to think about it in the context of some of the other babies and the multiple vial theories that we may be talking about. Because not only propylene glycol causes acute arrest phenomena. It also, number one, can accumulate to incredible quantities in infants and cause what we call hyper-osmolarity and seizures. This has been documented now in a recent report from the National Children's Hospital in Washington where vitamin preparations containing high concentrations of propylene glycoll were being used in hyper-elementation solution, and I will get you the reference; and where in fact it can act as a confounding variable when you think you are looking at toxicity from one drug you might in fact be looking at toxicity from the diluent. I was concerned last night and I got up again early this morning re-reading that this may be a problem.

THE COMMISSIONER: Before you get



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too concerned about this. This other drug, is it
detectable?

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THE WITNESS: It is detectable by
gaschromatography mass spectromotry.

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THE COMMISSIONER: I mean has anyone attempted
to detect it in any of these --

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THE WITNESS: As far as I know
no one has looked for it.

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THE COMMISSIONER: Well, if the
result of an overdose of digoxin is not death
from digoxin but death from some other drug does
it really make that much difference?

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THE WITNESS: It makes a
difference in interpreting timing dramatically.

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THE COMMISSIONER: I see. All right.
THE WITNESS: Because toxicity
from an overdose of propylene glycol is rapid,
and toxicity from an overdose of digoxin may be
slow.

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THE COMMISSIONER: I don't want to
stop you, but in the last 24 hours investigations -
I found disturbing.

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THE WITNESS: I found it
disturbing to go back in the chart and found
something I had not found before, it happens all



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the time to us.

THE COMMISSIONER: All you found was that there was a dose of lasix, isn't that it?

THE WITNESS: And in another baby as well.

THE COMMISSIONER: No, no, but that is all you found?

THE WITNESS: We found at least --

THE COMMISSIONER: We have now got ---

THE WITNESS: ... two of the babies arrested very shortly after administration of an IV dose.

THE COMMISSIONER: We have now got digoxin coupled to this other drug that is contained in digoxin and therefore we are now going to have the baby dying because of a reference to a dose of lasix, we are now going to have the baby dying of some drug that is contained in the vial of digoxin, is that right?

THE WITNESS: In the complexity of medicine we have to accept every possible hypothesis. I am not asking you to accept it.

THE COMMISSIONER: Yes.



F-5

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2 THE WITNESS: That is not my
3 responsibility.

4 MR. SCOTT: If I might make a
5 submission. It is just midweek but we are all
6 getting tired. I am getting tired, Mr. Lamek
7 says he is not.

8 I think it is important to
9 emphasize the position of the Hospital with
10 respect to this evidence. I don't want to test
11 anybody's patience, but I think it is important.
12 We don't know the answers to the questions that
13 you have been asked. It is for you to decide
14 them.

15 The two theories are murder and
16 whether you will name names, to use my phrase,
17 it is for you to decide later. Or some
18 accidental or medical theory. If the first
19 so be it; if the latter we will know within
20 five years. In other words as we study these
21 records and as we learn more about medical
22 science we will have the second answer, if that
23 be the right answer, within five years.

24 Our obligation to you, and it is
25 the obligation of all counsel, is to see that
in selecting between those alternatives you don't



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overlook any fact so that in five years you
can live with your conclusion, as the right
conclusion. What we have here is a matter of
concern that has come to this doctor's attention.
it would be easier just to ignore it because it
is late and why have we come to this.

THE COMMISSIONER: I don't
suggest ignoring it.

MR. SCOTT: No.

THE COMMISSIONER: I am just
suggesting that we don't have theories spouting
for it at the very moment. Almost, since he
started his evidence, that's all, it really is
not thought out.

MR. SCOTT: I am not prepared to
say that.

THE COMMISSIONER: That is what
concerns me.

MR. SCOTT: I am not prepared to
say that and I think it is premature for anybody
to conclude that. What the doctor is presenting
to you is an observation he has drawn from the
chart. He is not saying it is the end of the
story; he is not saying it is an answer you are
going to have grapple with. He is saying that



F-7

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2 this is what you have, you have the physical
3 phenomena. That physical phenomena as he has
4 pointed out and he has discussed with me this
5 morning, is critical not with respect to the
6 murder theory, but it is going to be absolutely
7 critical if you are going to name names because
8 it has to do with time.

9 Now you can't, it will be your
10 business to reject the theory, or to say it has
11 no impact, on a scientific basis, or it was just
12 thought of at the last moment, or anything you
13 want to say. I think it is important that you
14 would hear it with, as you have had throughout
15 these hearings, with an indulgent ear,
16 conscious of the importance of this issue to
17 everybody and conscious of Commission Counsel's
18 desire and the desire of all of us to see that
19 you get everything that may bear on these
20 questions. I know we all want to go home, and
21 I want to go home.

22 THE COMMISSIONER: No, it is
23 losing the - I have forgotten what the
24 appropriate cliché would be.

25 MR. SCOTT: I will come to it
surely if it is an appropriate cliché.



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THE COMMISSIONER: You can help me with the cliché. The trouble is there is something about, forest and trees, and wheat and chaff and that sort of thing that people have been presenting and we can't - to me, somehow a speculation which may have come to somebody's attention at three o'clock in the morning, or just before, is not really what I want. What I want is I want something thought out, I want something with some concrete evidence, that there is some possibility that I might accept. How I can accept this one is beyond me.

MR. SCOTT: Mr. Commissioner, the whole exercise is speculative.

THE COMMISSIONER: Yes.

MR. SCOTT: The murder theory is speculative. The other theory is speculative. What you have to do is take the facts and weigh them. Now whether you can answer the questions, it may not be possible for you to answer the questions. But to say that a professional man reviewing the chart and seeing something for the first time and putting two and two together is speculative, is, I suppose



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right in the best scientific tradition, that is what scientists do. Now, it isn't what lawyers do, but it is what scientists do and I think we have to be fairly indulgent about this exercise insofar as you are seeking scientific assistance to respond to a legal problem.

THE COMMISSIONER: All right.

MR. SCOTT: And I hope you will tolerate it just for a short while.

THE COMMISSIONER: Yes, I will, I will. Carry on please Mr. Lamek.

THE WITNESS: Again if I may Mr. Commissioner, it is not again trying to bring up something that is going to be misleading or confusing. In fact I have been thinking, and worrying, and trying to understand these things for over a year.

The fact that something new comes along is in fact the nature of science, and the nature of thinking, and the nature of our own naivety which I admit to fully.

THE COMMISSIONER: I don't want to suppress your investigation, I would just like the investigation to be perhaps a little more sophisticated before it is presented to me, that is



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all, that is all I was trying to say.

THE WITNESS: I understand.

THE COMMISSIONER: All right,
carry on.

MR. LAMEK: Q. I am sorry, have
you ---

A. So the issue then becomes
a concern about what that lasix dose represented,
and might or might not be relevant to the digoxin
levels which we achieve.

Then we realize that the baby does
go into asystole, this is indeed an asystolic
arrest where there is no heart beat and there is
no - resuscitation in essence fails and then an
autopsy is done.

Is there anything in the autopsy
that helps me with respect to whether or not there
may be a problem with respect to the number that
we achieved, the 72?

The only problem I have with the
autopsy that might act as a confounder is something
that we will have to deal with later a bit with
the Estrella case and several other cases, that
being again the tremendous quantities of digoxin
within tissue compared to the amount of digoxin



F-11

1 within blood.

2 The autopsy report makes
3 specific reference and I looked through the rest
4 of the charts over time and was unable to find
5 again quite a specific reference to the degree
6 of resuscitation trauma which had occurred in this
7 baby. Now that again is no one's fault. What
8 happens during a resuscitation is that multiple
9 attempts are made, as we discussed before, using
10 intracardiac medications, which can damage the
11 myocardium; and furthermore an attempt was
12 made putting in a pacemaker in this child.
13 Every attempt was made to save this child's life,
14 including electrical defibrillation, putting
15 pacing wires in, multiple intracardiac
16 medications, even though the medication sheet
17 in this case doesn't list which were and which
18 were not intracardiac, in fact the autopsy has
19 puncture marks to demonstrate that they were
20 intracardiac medications.

21 What was striking in the
22 autopsy in this child is that there was a great
23 deal of trauma compared to some of the others
24 in that there were 75 millilitres of blood in
25 the left part of the chest, 20 millilitres of
blood in the right, and about 15 millilitres of



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blood within the damaged pericardial sac. This was indeed different than some of the other infants, in extent.

The question that has to be raised in terms of potential artefact is given that the blood sample is then obtained by placing a needle through a damaged myocardium, which already has exhibited damage from the resuscitation process, could some of the elevation in that blood level be due to damage to the myocardium. That is the only artefact concern that I have in this infant. How probable is it again, we don't know, I think it has to be considered as one possible artefact.

Q. Could I interrupt you just for a moment Dr. Spielberg?

A. Yes.

Q. What is the basis for saying blood was drawn from the heart for this sample?

A. I believe it was. I am not actually sure, if it is a sagittal sinus sample ---

Q. My recollection of the evidence which is supported by Miss Cronk.

A. What does it say?



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Q. And I put it no higher than that is, and it is a recollection only, is that the pathologist's evidence was that this sample was taken at autopsy from the inferior vena cava?

A. From the inferior vena cava?

Q. Yes.

A. Okay. If that is the case that indeed makes that issue somewhat less relevant, except to the extent that during resuscitation some may have leached out but in the presence of asystole it decreases that probability.

Q. Yes.

A. Now then what are we left with with the level --

Q. I am sorry.

A. Thank you very much, I certainly don't mean, it was my understanding it was a cardiac sample I am glad to be corrected.

Q. I don't guarantee that, that is my recollection of it.

MISS CRONK: That is what Dr.Cutz said.

MR. YOUNG: Dr. Taylor said that



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as well.

MR. LAMEK: Thank you.

THE WITNESS: Because that is the only thing that I can find in the autopsy of this infant to suggest the potential of artefact. If in fact that is not the case then I think we are left with trying to explain how the blood level got to 72 in terms of administration.

Q. Yes.

A. And again basically, I don't think it is worth going through the same calculations again, the same type of constraints hold. A small amount of digoxin given in accident or intentional prior to arrest or intra arrest, going all the way on up to the multiple vials being administered with obvious intent in that would not have been accidental.



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Q. Sure.

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A. What corroborative evidence

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do we have one way or the other to support either theory. As we indicated, our tissue levels can't help us. They were very low but I would be loathe to argue that they were low in fresh tissue because of the tremendous variability. So, the low value doesn't help us one way or the other.

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What can we say with respect to the other possibilities, multiple vials again. The only things against multiple vials again would be one of the discussions we had yesterday with respect to Justin Cook. The improbability of cracking all the vials open, the improbability of being able to push that volume and coupled with the volumes which would have been too much fluid overload for the child as well as the issues now with respect to the diluent in the compound which probably would have caused more rapid more arrest as well as hyperosmolality.

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So, I think again multiple vials becomes less likely. And then we are back to the constraints of a 70, with one addition that we have to add in. This is 70 postmortem. We do not know what the premortem is and we now have to add on a multiplier factor to try to get back at premortem



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2 levels for, in fact, the blood level prior to death
3 may have been 26, which would be about one-third that
4 neighborhood of what the postmortem level was.

5 I think somewhere between two and
6 three-fold multipliers are reasonable numbers to
7 use, again, saying that some babies there
8 will be no increase and the 72 may have reflected
9 premortem. In other babies it may have been lower.

10 Q. Yes.

11 A. Lower to the therapeutic range,
12 I doubt it very much. So that we have to accept
13 higher numbers and presumed administration of some
14 digoxin barring some artefact that we just don't
15 understand. That being the case, again, we are
16 stuck with the same kinds of broad ranges of
17 considerations of amounts. The vast volume theory
18 I think is not an acceptable theory. Smaller volumes
19 that still are potentially toxic, which may have
20 contributed to the arrest or may have contributed
21 to the lack of the success during the resuscitation
22 are indeed entirely possible and I have no independent
23 way of ascertaining why they were given or how they
24 were given.

25 Q. Sure.

THE COMMISSIONER: This multiplier



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factor that you are talking.

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A. Yes.

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THE COMMISSIONER: We have heard about that from time to time. I don't know that we have had any -- has there been any appropriate study on it? Surely the Hospital for Sick Children would have been an ideal place after this disaster to determine that question, whether there was or was not a multiplier. I take there has been?

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THE WITNESS: I don't have actually the Hospital for Sick Children's numbers. I have Dr. Hastreiter's numbers.

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THE COMMISSIONER: Yes.

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THE WITNESS: As published.

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THE COMMISSIONER: That's evidence we haven't had yet, I guess.

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THE WITNESS: Yes. I believe you have that manuscript, Mr. Lamek.

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MR. LAMEK: The one you gave me?

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A. Dr. Hastreiter's most recent.

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Q. Yes.

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A. Interestingly, again, his numbers in children tend to be slightly higher than the numbers in the published adult literature. Most of the data we have are as adults. This is a



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2 study in children. He gives a range, a mean of about
3 3.2 fold increase in his children and again with a
4 lot of variability because in fact some children
5 won't go up and other childrens' will go up higher
6 than that. I think it is a fair acceptance of
7 two to three-fold.

8 THE COMMISSIONER: You don't know
9 what the -- presumably each of these children were
10 children who automatically had -- every dying child
11 had digoxin administered, at least, whether or not
12 it was tested for digoxin.

13 THE WITNESS: Yes.

14 THE COMMISSIONER: All of those who had
15 been on digoxin would have been tested before.

16 THE WITNESS: Yes.

17 THE COMMISSIONER: Surely some figure
18 would have come out of that.

19 THE WITNESS: I don't have those
20 available. I assume in all of the data that had
21 been collected in pathology that would be ascertain-
22 able. I don't have them.

23 MR. LAMEK: Perhaps we can address that
24 after the break, Mr. Commissioner.

25 MR. ROLAND: Mr. Commissioner, I take
it you are talking about the multiplier effect between



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2 life and death.

3 THE COMMISSIONER: That's right.

4 MR. ROLAND: There have been papers
5 put in on that.

6 THE COMMISSIONER: Has there?

7 MR. ROLAND: I referred to it, to that
8 paper in particular in discussing that with Mr.
9 Cimbura and I am trying to find which one it is
10 but there certainly has been evidence put in and
11 some papers put in about that multiplier effect.

12 THE COMMISSIONER: Well, I know we
13 have had a great deal of reference to it. I didn't
14 know that we had a paper on it.

15 THE WITNESS: And we certainly can
16 enter the manuscript that I provided to Mr.
17 Lamek as well.

18 MR. LAMEK: Yes.

19 THE COMMISSIONER: Dr. Hastreiter
20 is to give evidence?

21 MR. LAMEK: Dr. Hastreiter is to give
22 evidence, that's correct.

23 THE COMMISSIONER: Yes.

24 MR. LAMEK: Q. First before we break,
25 Dr. Speilberg, on that particular point can I just
clarify something for my own purpose?



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A. Sure.

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Q. I guess I was taught at a very early age that nothing comes out of nothing. I take it that the multiplier effect in serum that we are talking about has been observed to have occurred with some frequency in postmortem is the flip side of the unbinding that you were talking about yesterday that occurs after death.

A. One of the explanations for how it happens is that it is lost from tissue.

Q. And back into serum?

A. And back into serum, yes.

Q. So, it is not that the digoxin in the serum suddenly of its own accord starts propagating and multiplying.

A. No, there is conservation of mass and energy in the universe.

Q. Yes, thank you.

A. I hope.

THE COMMISSIONER: Well, yes, but I take it that this multiplier effect, of course, will be dependent upon a lot of things such as time, the time before death and the time after death and I just wondered if no one had made a study of that, and apparently there has been.



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2 THE WITNESS: Oh, there are several,
3 probably at least half a dozen publications
4 in the area, possibly more.

5 MR. LAMEK: Yes.

6 THE COMMISSIONER: Do you want to
7 break?

8 MR. LAMEK: If we may.

9 THE COMMISSIONER: All right, twenty
10 minutes then.

11 ---Short recess.

12 ---Upon commencing after the break.

13 MR. ORTVED: Just on that subject of
14 the multiplier, some of the earlier exhibits that
15 were filed, for instance, Exhibit No. 20 talks
16 about that, Mr. Commissioner, 20, 21. They have
17 reference to the multiplier effect.

18 THE COMMISSIONER: Yes, thank you.
19 I have received a letter from Mr. Olah, a copy
20 of which has gone to many other counsel. I intended
21 to reply to it but I don't intend to reply to it
22 until Mr. Olah is here. Oh, here he is.

23 I received the other day a letter
24 from Mr. Olah which he asked to become part of the
25



1
2 record. I don't have it with me at the moment but
3 it will become Exhibit 220.

4 ---EXHIBIT NO. 220: Letter dated October 22, 1983,
5 Attention The Honourable Mr. Justice Samuel Grange
6 from John A. Olah.

7 THE COMMISSIONER: A copy of this
8 letter has been given by him to several other counsel
9 and, of course, it will be available to anyone who
10 is concerned. I don't believe there is any strict rule
11 requiring it, but we have given Mr. Olah and all other
12 counsel concerned the substance of the evidence that
13 we intend to adduce respecting any possible mis-
14 conduct on the part of their clients. There are,
15 therefore, no particulars to provide.

16 We may or may not give a special
17 notice to any person under Section 5(2) of the
18 Public Inquiries Act. We may also at some point
19 reach the conclusion that there is no possibility of
20 a finding of misconduct against a particular person.
21 On that event, we shall notify the person concerned
22 and recommend that public funding of counsel cease.

23 Obviously, if any additional evidence
24 should come to hand it would be fair to pass it on
25 to the person concerned and that is our intention.
We cannot be sure, however, that incriminating



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2 evidence will not be revealed for the first time
3 in testimony and counsel must be prepared to deal
4 with such evidence as it arises.

5 It is not our intention to recall any
6 witness unless it can be demonstrated that he has
7 fresh relevant evidence to give. Nor is it our
8 intention to adjourn the hearing to permit counsel
9 to consider his client's position. It is my
10 view that he should have been considering that
11 position from the beginning and should have kept it
12 constantly under review.

13 Having said all that, however, it is
14 clear that my interpretation of Section 5 of the
15 Public Inquiries Act does not meet with unanimous
16 approval. I will therefore entertain any argument
17 on the question at the same time as the argument
18 on the production of the police report.

19 Yes, all right. Yes, Mr. Brown.

20 MR. BROWN: Excuse me, Mr. Commissioner,
21 before you go on.

22 THE COMMISSIONER: Yes.

23 MR. BROWN: You have indicated that
24 you have given substance of the evidence to parties
25 concerned. There is one report which we have
not yet received, I believe.



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THE COMMISSIONER: That's the police

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report.

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THE COMMISSIONER: Have we got such
a thing?

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MR. LAMEK: Mr. Commissioner, in the
first place I am not sure that it goes to a question
of evidence against anybody but it has or is being
copied and will certainly be distributed. There is
no problem about that. That will be distributed
to all counsel.

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THE COMMISSIONER: Yes.

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MR. BROWN: Well, the timing of
distribution is of some concern. If it can be
distributed as soon as possible that would certainly
be appreciated.

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MR. LAMEK: Certainly.

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THE COMMISSIONER: Yes, all right.
Yes, Mr. Olah, I think was up first. Yes, Mr.
Olah?



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MR. OLAH: This is in response to my
formal submission or my letter.

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The immediate matter that concerns
me is this, Mr. Commissioner. When you indicated
a deadline of November 1st for written submissions
that encompassed two matters that were outside my
concerns. Do I take it that November 1st is the
deadline for submissions with respect to notice?

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THE COMMISSIONER: No, no, that is to
be oral argument.

MR. OLAH: That's the oral argument.

THE COMMISSIONER: That's the police,
and I haven't heard.

MR. YOUNG: Mr. Brown and I are
attempting to find an agreeable date.

THE COMMISSIONER: Yes. Well, when that
is we will have that at the same time and that is
not to be written, that is to be oral. The main
reason I wanted oral is, I want somebody to tell me
how I could conceivably conduct this inquiry in any
other way than the manner in which it is now being
done. That's all. So, if there is some other way.
I mean, I don't mean by that, I mean on that
particular issue. I don't want to hear about
the rest of it, thank you very much, that you can



12 2 write a book about and publish someplace else.

3 I want to simply know how it is possible
4 to conduct a hearing under Section 5 by waiting until
5 something happens or all of us gets together and then
6 all of a sudden you say we recall all of the
7 witnesses and start again. That is not my intention.
8 I am too old, I wouldn't last.

9 MR. OLAH: Well, I wasn't suggesting
10 that generally, I was suggesting it in the particular
11 situation that we were met with and I would be
12 pleased to make submissions on that.

13 Just so I am clear and I understand
14 your ruling, sir. Is it a ruling or a purported
15 ruling?

16 THE COMMISSIONER: Yes, all right.

17 MR. OLAH: It is a release.

18 THE COMMISSIONER: It is an answer,
19 if you like, to your letter.

20 MR. OLAH: It is a response. I take
21 it, just so I am clear.

22 THE COMMISSIONER: Just trying to save
23 stamps.

24 MR. OLAH: Well, I just want to be
25 clear. We've got no formal ruling, it is merely an
advance ruling of some kind.



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2 THE COMMISSIONER: I told you what
3 my views are. I suppose that is not a ruling.
4 I am quite prepared to hear any argument that anyone
5 wants to give me on Section 5, but at the moment I
6 have said we may or may not give a notice. We may
7 at the same time also give what you could call a
8 non-notice, that is, that you are no longer con-
9 cerned in this matter, please go away. If you get
10 that, you can hardly complain about not getting
11 a notice.

12 MR. OLAH: That's all I would like,
13 frankly.

14 THE COMMISSIONER: But I'm not prepared
15 to give it today.

16 MR. OLAH: Thank you.

17 THE COMMISSIONER: All right.

18 MR. OLAH: Thank you very much.

19 THE COMMISSIONER: Now, you had
20 something, Mr. Ortved?

21 MR. ORTVED: No, I decided to abandon
22 it.

23 THE COMMISSIONER: Excellent. All
24 right. Okay, now, Mr. Lamek.

25 MR. LAMEK: Q. Dr. Spielberg, just one
other thing, if I may, on that multiplier about which



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we have heard so much, about which we were speaking
just before the break.

A. Yes.

Q. You have told me that at
least one explanation that is advanced for the
observed elevation postmortem digoxen concentra-
tions in serum is that it is what I would call the
flip side of the unbinding from tissue.

A. Yes.

Q. That is known frequently to
occur postmortem. You told me yesterday that
generally speaking the unbinding is a continuing
process after death for a period of time. I take
it, therefore, that if the unbinding is the flip
side of the serum elevation that with increasing
time from death one might expect to see an increasing
concentration in the serum.

A. In a general sense, yes.

Q. In a general sense, yes,
thank you.

Now, can we just for a moment
explore your evidence before the break that flowed
from your observation that a dose of lasix was
administered to Allana Miller very, very shortly be-
fore her death.

A. Yes.



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Q. Can I ask in the first place why you assumed administration of a dose of digoxin close to the time of arrest?

A. The question really arises from the same considerations which we have been talking about. In other words, how far before or after a specific event can we explain a blood level based on amount of administration.

Q. Yes.

A. So that again we are working in very broad time frames, as we have discussed, one hypothesis being that it was very shortly before the time of death, so that we are somewhere again along that alpha phase of distribution.

Q. And the possibility that what was believed to be lasix was in fact not lasix but something else, for example, digoxin, becomes relevant if you are assuming for the purpose of one explanation of the level an administration virtually immediately before the arrest?

A. Yes, this would be the concern, yes.

Q. Yes, of course. But there is nothing in the situation that compells that assumption, is there?



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A. No, the concern is that when, for example, we look at an event occurring in clinical care and try to make an association with administration of a drug, at least one of the important criteria that we look at is a temporal association, and there is something rather striking here between the time of administration and the time of death. However, the child, as indicated, was getting worse during this whole period of time, and thus, one potential place where the digoxin might have been administered is in substitution for lasix. It could have been administered before; it could have been administered after.

Q. Yes. So the timing of the lasix dose has relevance only to the one hypothesis, that the administration of whatever it was, digoxin, occurred shortly before arrest?

A. Yes.

Q. And of course, if the administration of digoxin occurred 30 minutes, 45 minutes, an hour before that, then we have got to look somewhere else other than at the lasix?

A. Certainly.

Q. Yes. Now, the other suggestion -- can we just follow that for a moment, though. You will have to help me here. What is a



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standard size dose of lasix for a child of 11, 12
months, Allana Miller's age?

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A. This was about 6 milligrams.

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Now, unfortunately, I do not know how the lasix was
being administered on the ward at that time. The
standard preparation of lasix is an IV -- an ampule
which contains 10 milligrams per ml.

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Q. Yes.

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A. Okay. So that if one were
giving it straight, we would be talking about the
neighbourhood of, I suppose in this situation, about
6/10ths, a little more than half of a ml.

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If we are talking about diluted drug,
which often is done, and I do not know whether it
was being done on 4A/B at the time -- we did at
our Hospital at that time, I do not know whether
it was being done here -- then the volume could have
been considerably greater. So if we could get that
information in terms of how the drug was actually
handled, we could answer that more directly.

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Q. And that may or may not bear
upon the likelihood of drug error?

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A. Precisely, and that would be
an important consideration.

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Q. What we do know, however, I



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take it, is that at some point in time Allana Miller probably received an unprescribed dose of digoxin; is that fair?

A. I think that is our best hypothesis at this time, yes.

Q. Whether it was instead of the lasix or in addition to the lasix or anything else, a strong probability is that an unprescribed dose was administered to the child?

A. On the basis of the evidence, yes.

Q. Now, you have suggested, as I understand you, that even though an unprescribed dose of digoxin was administered, one way of postulating that that occurred shortly before the arrest is to focus upon the propylene glycol, which is found in the parenteral digoxin preparation, because do I understand this correctly, one of the difficulties of positing an administration of digoxin very shortly before the arrest, the arrest consisting of asystole, is that -- well, we do not have levels in the tissues to contend with, do we?

A. We do not, unfortunately.

Q. Because we do not know what they were. They may have been high; they may have



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been low?

A. Yes.

Q. We can still posit administration of digoxin shortly before arrest if it was not in fact the digoxin that was active in causing the arrest, because digoxin would take some time to distribute to the degree to have the pharmacological effect of causing arrest or death?

A. The general time course one would expect from the effects of, say, propylene glycol would, in general, with a range, be expected to be somewhat more rapid than the effects of digoxin. It depends very strongly on the rate at which the propylene glycol has been administered, because you can administer reasonably large volumes slowly without this toxicity, whereas the same volume administered very rapidly causes more toxicity.

Q. Define large volumes?

A. Again, I am going to have to go back and get data. For instance, in an adult, you can cause an arrest by administration IV push too rapidly of a solution such as Valium or Dilantin containing the same amounts of propylene glycol, a half ml or an ml in an adult. So it does not take very much if it is given very, very rapidly as an



H6
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2 IV push.

3 Often the way lasix is administered
4 to patients is as a very rapid IV push because one
5 seems to get different effects. Again, with lasix,
6 depending on how it is given, and often lasix is
7 given as a push, whereas other medicines may be
8 given more slowly and more gradually.

9 Q. Let me understand you, however.
10 Your suggestion with respect to the effects of
11 propylene glycol does not necessarily assume an
12 error as between lasix and digoxin, does it?

13 A. There is no propylene glycol
14 in lasix.

15 Q. No. What I am saying is you
16 do not have to substitute the digoxin for the lasix
17 dose in order for your thought about propylene glycol
18 to be triggered?

19 A. I think it is a consideration
20 that has to go into the formulation of any of the
21 considerations and any of the timings.

22 Q. Your suggestion, if I under-
23 stand you, is that a dose of digoxin, if administered
24 too quickly, may produce the toxic results you have
25 talked about from the propylene glycol content in
that preparation?



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A. Yes.

Q. All right. Now, I take it what pushes you towards the possibility that that may have occurred in substitution for the lasix is (a) the fact that you understand lasix is frequently administered via IV push?

A. Rapidly, yes.

Q. And rapidly, and I take it that digoxin normally is not?

A. Yes.

Q. And secondly, there have been no doubt hundreds of thousands, millions of doses of digoxin administered in this same parenteral preparation with the propylene glycol without the temporal relationship that you are dwelling upon here?

A. Certainly, and in the doses that we would use it therapeutically, again the total volumes, for instance in a baby this size who is ordered 32 micrograms, we are talking about a small volume of drug that will be gradually dripped in. So it is a different situation, certainly.

Q. So you say we must consider the possibility that what was considered to be a dose of lasix very shortly before the arrest may have been, by error, administered as digoxin, given



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digoxin instead of lasix?

A. I think that has to be considered.

Q. It is a possibility?

A. Either by error or intent.

Q. Yes. And as to that, of course you can express no particular view?

A. I cannot separate the two.

Q. Is there anything further, Doctor, in which you are able to help us with respect to Allana Miller, or is that the extent of the thoughts or opinions which you, as a clinical pharmacologist, feel able to express on this child?

A. I believe that is about as far as we can take the discussions, the minimum and maximum amounts that might have been given, and that is about, unfortunately, as far as we can take it, I believe.

Q. There is just one question. You mentioned quite properly, very properly, the prior history of arrhythmias with this child.

A. Yes.

Q. Is one able to generalize as to whether a history of arrhythmia may make a child more susceptible to the toxic effects of digoxin?



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A. Yes. Again, in a general sense, patients who do have arrhythmias of a variety of different types might be thought to be more susceptible to digoxin further induced arrhythmias perhaps at lower blood levels than in another patient. That is certainly possible. That is why we said, for example, even in a patient who has a therapeutic blood level of digoxin and has increasing arrhythmias, you really cannot be sure that it is not the digoxin and you might want to cut it back regardless.

Q. And does it follow from that that it is a function of the amount of digoxin which is distributed to tissue, and therefore, a child with what we might call a sensitivity to digoxin of the kind we have described may exhibit toxic responses at relatively low levels of transportation of the drug to the heart?

A. Yes. We know that for blood level in any case. We do not really know the correlation with what is in the myocardium, because again that study has not been done. But certainly children, or adults, for that matter, with therapeutic blood levels might manifest toxicity of digoxin if their myocardium was, as you say, predisposed to that.

Q. I guess what I am getting to



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is this, Dr. Spielberg. Whenever and however this probable dose of digoxin was administered to Allana Miller, because of her predisposing condition, is it likely that her response to that dose occurred at a higher point on the alpha phase curve than perhaps a child without that predisposition might have?

A. In a theoretical sense, yes.

Q. Leaving still 78 nanograms to be discovered in the blood post mortem?

A. Certainly.

Q. Okay. Can we then go to Kristin Inwood, working backwards in time.

A. Let me just exchange charts.

Q. Dr. Spielberg, I am reminded by Miss Cronk that I did not ask you to state minimum and maximum doses in Miller. I take it that the range would be as in Cook?

A. We are talking basically the same kind of range.

Q. Less than a pediatric vial in one extreme to multiple vials at the other?

A. Yes, and with the sort of reasonable middle ground, again, we are talking an adult vial or less, that sort of middle ground range,



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but again with a great deal of variation and spread.

Q. But I take it, Doctor, that in the Miller case, unlike the Cook case, the absolute minimum dose is not as unlikely because you do not have to account for very high tissue ---

A. Yes, exactly, and under these circumstances, in fact, we could be talking about as little as the minimum because the baby was already on digoxin and the finding of any digoxin in the myocardium would have been expected to be from her prior treatment.

Q. Now, when we get to Kristin Inwood, this again is a child on digoxin therapy; remember from your review of the chart?

A. Yes.

Q. It appears from page 75 of the chart that the dose that had been ordered was .006 milligrams?

A. Yes.

Q. To be administered orally twice a day on the basis of .005 milligrams per kilogram?

A. Okay, sure, 5 micrograms per kilogram.

Q. 5 micrograms, same thing?



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A. Correct.

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Q. And it was Dr. Kantak who

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wrote that order. Now, page 81 of the chart, and I

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am afraid your chart is like mine, the pagination

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is not very clear.

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A. No, I have that page.

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Q. You do?

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A. Yes.

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Q. The biochemistry report?

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A. This is the biochemistry

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report, yes.

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Q. It appears that in a sample

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drawn at 9:00 a.m. on the 12th of March, a digoxin
level of 2.6 was recorded?

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A. Yes, that is correct.

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Q. Now, that morning at 6 o'clock,

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and this appears on page 76 of the chart, that

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morning, prior to the drawing of the sample, it

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appears that Dr.Kantak again had ordered that dig.

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be held for four doses and that a level be obtained
that day?

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A. Yes.

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Q. And when the level was in fact drawn produced a result of 2.6.

A. Yes.

Q. Doctor, upon your review of the chart did you see anything to explain the order to withhold digoxin for four doses, that order having been written at 6 a.m. on the morning of March 12.

A. There appears to have been a medication error in digoxin administration in this infant. In fact, my understanding is that she received a dose in the neighborhood of about three times the volume that she should have received, in a prior dose.

Q. That is right.

A. And that this was noted by the nurse, she apparently realized at some point and I don't know exactly when after administration that this had occurred. The incident report was indeed filed and an appropriate response under such circumstances would be to obtain a level, withhold further administration until one sees where things are heading.

Q. You are entirely right, I had forgotten the medication error there. The order, however, seems to have been followed from the



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med sheet, does it not?

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A. Yes, that is correct.

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Q. This is at Page 87 of the

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chart, and the level was taken that morning disclosing
as we have said the level of 2.6.

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A. Right.

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Q. Which I suppose is slightly

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elevated from that that one would normally see in
a therapeutic monitoring program.

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A. Yes.

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Q. Not grossly elevated.

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A. No, and certainly in fact we

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have many infants who we maintain in the 2.5 to 3
range when they have been followed for long periods

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of time, and we find out that level is appropriate for
them, it is certainly not an extraordinary level

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at all.

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Q. If we go to Page 63 of the

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chart we find the nursing note of Nurse Jones, she

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reports half way through that note at 2 a.m.

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A. Yes.

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Q. The monitor strip showed

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abnormalities; notified the team leader; resident
called; again lasix was given three milligrams

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IV by the resident. Tachycardia up to 200 followed

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2 and the babe was irritable with a number of
3 plus signs and I take it that means very,very
4 irritable.

5 A. Presumably so, yes.

6 Q. And at 0230 A.M. Code 25 is
7 called and the child could not be revived.

8 A. Yes.

9 Now, one additional point, this
10 Code was called not for asystolic, but in fact for
11 bradycardia from the resident's note, I believe, on
12 Page 62. So we have a slightly different
13 clinical presentation again, one of tachycardia
14 then bradycardia, falling blood pressure.

15 Q. Yes.

16 A. And a response by the arrest
17 team.

18 Q. Now, at autopsy, and the
19 report is found at Page 20, I believe, of the chart.

20 A. Yes.

21 Q. Several findings including
22 an area of subendocardial and myocardial
23 necrosis in the left ventricular.

24 A. Yes.

25 Q. So far as the data
are concerned, as you know from Dr.Cimbura's report,



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a serum level of 14 nanograms per millilitre
was recorded, apparently in a post-mortem sample.

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A. Correct.

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Q. There was no fresh tissue available for sampling, but levels of, in terms of digoxin, 230, 80, 300, were recorded in fixed heart tissue.

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A. Yes.

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Q. I suppose I first have to ask you, Dr. Speilberg, if you regard the 491 level as a real level.

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A. Yes.

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Q. Do you?

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A. I question it strongly.

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Q. All right, on what basis?

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A. There are several problems with the sample. The most concerning is that we do not first have good evidence as to exactly how the sample was obtained. There are not those records available. This has particular relevance since, as you mention, the child had subendocardial necrosis of the heart and particularly since the microscopic examination at autopsy shows necrosis of one of the papillary muscles, these are one of the muscles that hold the valve leaflets in. Papillary muscle has a tremendous amount of digoxin in it. Such as if



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one were, for example, to stick a needle into the heart near that dying piece of tissue one might end up obtaining a tremendous amount of digoxin. Now, the trouble is we have no data whatever as to how the sample was obtained.

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The second problem is that whatever the sample is, and we can't even be one hundred percent assured that it is serum and not perhaps a little piece of tissue plus serum, because the sample was stored for a very long period of time under circumstances of having been left in the back of a refrigerator.

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Now, there are several things that one has to worry about in that regard, even if it is kept in a self-defrosting freezer, because self-defrosting freezers remain self-defrosting by heating and cooling, coming up above freezing and going back down. When one has a very small sample for a biological assay, or for a chemical assay, that means that the sample is defrosting and freezing and defrosting and freezing periodically, if it is a small sample.

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The second point is that if we do not know exactly how the sample was kept, there is always the possibility of some degree of evaporation,



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2 or loss of volume, and as such whatever is present
3 that is non-volatile the concentration of that
4 will go up.

5 Finally, the possibility exists of
6 cross-contamination of a sample that is kept in the
7 back of a fridge and other things being moved around.
8 Basically we just don't know how the sample resided,
9 shall we say, for the six month interval.

10 I am more concerned about where the
11 sample was obtained from, frankly, because we are not
12 really sure what it represented; serum, whole blood,
13 blood with a little piece of tissue sucked in when
14 the sample is obtained, we just don't know. That
15 obviously has to place maybe a question on interpreta-
16 tion of this.

17 The storage issue has been looked
18 into somewhat, I gather, by Mr. Cimbura, by trying
19 to mimic what would happen if you stored a serum
20 sample, you know, under refrigerated circumstances
21 and such. The study in general I believe, I haven't
22 seen the actual numbers, in general I believe shows
23 no tremendous changes under those circumstances,
24 there was also some heating that went on and such.

25 Q. Yes.

A. But that is an artificial



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circumstance where we are taking known serum and adding a known drug that hasn't been metabolized, hasn't been in the patient, etc. While I think it helps us a little bit to suggest that storage per se in an optimal sample may not be a problem, I have major concerns that this is not an optimal sample.

Q. Even though it came from your hospital?

A. Certainly. Samples obtained under clinical circumstances are fraught with hazard.

Q. I would tee it up that high I am not going to hit it, Doctor. All right, you have some severe doubts about the reality of the number because of the unknown or murky history of the sample.

A. Yes.

Q. Do you go so far as to say you can really base no hypothesis on that number?

A. No, we cannot ignore it.

Q. All right.

A. To ignore it denies the possibility that something else indeed may have happened, and we cannot do that, so we have to deal with it.



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2 Q. All right. Let us accept then
3 that for the moment the hypothesis is that a real
4 number, registered in post-mortem serum, and
5 tell me what if anything you do with it in that
6 situation.

7 A. Well, then again we have to
8 deal with several possible features.

9 First again let us assume that it is
10 real, that it is indeed 491 postmortem.

11 Then we have to deal with what we
12 have spoken about before the issues of multiplier
13 factors, so that 491 in effect could be three-fold
14 less, or in the neighborhood of 150.

15 Q. 150?

16 A. Regardless, we are talking
17 about extraordinary numbers.

18 Q. Yes.

19 A. Now how can those extraordinary
20 numbers be generated? Again, the third hypothesis
21 is that administration of digoxin, accidental or
22 intentional, regardless of motive, that the child
23 indeed received an excessive amount of digoxin.
24 Where could this have occurred and is it at all
25 reasonable to think about the kinds of amounts that
we are talking about?



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3 To get to 491, which we will accept
4 for the moment as a valid number, the very least,
5 the very least amount we are talking about here is
6 already getting up to about, and we are guessing,
7 really, in the neighborhood of 50 micrograms; that
8 would be the very least amount of drug that could
9 be given to achieve that number, assuming again
10 cessation of circulation when the drug was given,
11 or very close to that time, with no distribution.

12 Q. Okay. Let me understand you.
13 For the purpose of this exercise you are not only
14 assuming the reality of 491.

15 A. Yes.

16 Q. You are equating it to an
17 ante-mortem level.

18 A. Yes. We will accept the number
19 for the moment.

20 Q. It seems to me you can accept it
21 and at the same time by applying a divisor.

22 A. Okay.

23 Q. Let's do it on both bases,
24 let us take 419 ---

25 I think we have to again
because some patients may go up and some
patients may not.



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Q. Of course.

3

A. To be fair we have to.

4

Q. First a real number and represent-
ing an ante-mortem level, the moment immediately
before death.

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A. Right.

7

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So the moment of immediately before
death we are talking in the neighborhood of about
50 micrograms being administered. That is about
the equivalent of a pediatric vial, one full
pediatric vial of digoxin or a fraction of an adult
vial. That is the acute situation, again no distribu-
tion whatsoever.

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Then when we are talking about getting
down to sort of the top of the alpha curve now,
minutes later; we are talking in the neighborhood
of about one and one-third, 1.3 milligrams of
digoxin. Here we are already talking about several
vials of digoxin, 2-1/2, say, of adult digoxin.

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If we are considering this at steady-
state, assuming a volume of distribution of
15 litres per kilogram, we are then talking in the
neighborhood of 18 milligrams, this is 36 vials of
adult digoxin, it is 360 vials of pediatric
digoxin. This baby with 2.6 kilograms ---



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Q. I don't think you need to
pursue that by hypothesis any further.

4

A. It is hopeless.

5

Q. That is to produce 491 as a
steady state number.

6

7

A. As a steady state, yes.

8

The volume would have literally drowned the infant
before the digoxin got in, particularly in an infant
with congestive failure such as Kristin Inwood was.

9

10

11

Now, what about the intermediate
values, this is a big range because again we don't
know timing, we only know final result and now we
have to talk about amount.

12

13

Q. Yes.

14

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A. And again we are talking about
a very broad range from an adult vial to a pediatric
vial to several adult or pediatric vials.

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If we talk about the multiplier issue
and take the value down three-fold, then we are
talking about one-third less digoxin required to
produce each of those levels, or in the neighbor-
hood of, say, 15 micrograms to produce at the very
minimum a central volume of perhaps .4 milligrams
which is less than one adult vial for the central
type compartment issues. Then about six milligrams



1
2 for the final concentration. So we would just be
3 taking each of these down by one-third on the
4 assumption that the blood level had increased three-
5 fold. So, again these amounts are reasonably large
6 except for the acute situation.

7 Q. Yes.

8 A. Now, what other evidence do we
9 have and how can we deal with timing? Again, here
10 we have a problem. The only medication we know that
11 was administered very shortly prior to arrest was
12 the intravenous lasix issue again. How long before
13 tremendous change in rhythm distrubance we don't know.
14 It had to occur some time, according to the note,
15 between and 2 and 2:30, because the baby started
16 developing symptoms that the nurse was very concerned
17 about at 2, and the final arrest was around 2:30,
18 I believe, is that correct, time-wise?
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Q. I would just ask you a

question there, Doctor.

A. Yes.

Q. Why do you assume lasix IV.

On page 76 I read Dr. Schaffer's order. He was
the resident on duty that night ordering lasix
3 milligrams PO.

MR. ORTVED: If you go to page 63.

MR. ROLAND: Page 63 the nurse's
notes says it is lasix IV.

THE WITNESS: 3 milligrams IV by
resident.

MR. LAMEK: Q. That is the nurse's
notes?

A. That is the nurse's notes,
sir, yes.

Q. Why would he order it one
route and give it another?

A. I think under these
critical circumstances one wouldn't give oral
lasix. The baby is quite sick now.

Q. Certainly that's what the
nurse records, yes.

A. There is major concern about
it and under those circumstances giving an oral



J2

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drug that would act very slowly by that route is unlikely. He may have intended that that might have been an on-going order if the initial IV dose worked.

Q. Yes, okay.

A. I can't speculate about that but clearly the nurse's note indicates IV and clinically under those circumstances - you know, certainly under those circumstances I would have given the drug IV.

Q. Yes, thank you.

A. So, that is the one drug that we know was given just before the arrest. So, conceivably if there was either an error or intent that is one time it could have been given. I think if we are to accept this number at all, even assuming a multiplier effect and the spectacular height that we are talking about, if we are to accept the number, then we have to say it would have had to have been very very soon prior to death. How soon, again, we are talking guesses and we really can't say beyond that. Those are the maximum.

Q. Let me understand. If you accept 491 as the real level.



J3

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A. Even accepting 125 as the level we are still down in^{the} neighbourhood where if that represents a central compartment we are still talking about a reasonably short period of time.

Q. Okay.

A. To have gotten to that point. Again, how short, you know, ten minutes, a half an hour, an hour, we just can't say, we just can't say.

Now, there is another confounder in this which we have to accept in terms of a potential artefact and that gets us back to the autopsy and the sub endocardial necrosis and the papillary muscle necrosis which occurred. Our problem is again we don't know where the blood sample was from but if it was from the chamber in which that phenomenon was going on, again, we would expect that baby's heart to have a great deal of digoxin in it simply because the baby was on therapy and in fact had received an inadvertent excessive dose and had a level of 2.6. So that we cannot rule out the possibility that the dying tissue in the heart contributed significantly to an elevated blood



J4
1
2 level.

3 This for example was testified
4 to in the situation with Gary Murphy where one of
5 the hypotheses as to how this child's post mortem
6 level had reached as high as it did was secondary
7 to, in essence, tissue dying along the way prior
8 to the time that the baby died. That, in that
9 situation being felt to be the most reasonable
10 explanation.

11 Here we have another baby in
12 whom certainly myocardial death was going on and
13 had occurred and might have contributed
14 significantly.

15 The problem is, we don't know
16 how to interpret the 491 because we don't know
17 where it was from and we don't know what storage,
18 et cetera, et cetera, would have done to the
19 sample. So, the possibilities are: intentional
20 or accidental dose of digoxin having been
21 administered to the patient presumably reasonably
22 shortly before death, which might have produced
23 such a level; artefact in the level itself even
24 at the time it was obtained, because of the dead
25 and dying myocardial cells or heart cells or,
lastly, that the sample is uninterpretable because



J5

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it may have contained a variety of things that we just don't know about and had been stored for this very long period of time.

So, I think basically in this infant we have at least four possibilities: accidental or intentional administration, artefact due to dying myocardium, which we have now seen in at least one other and now several other babies, or the possibility that the sample does not represent what we believe it to be.

Q. Okay Doctor, I think that is helpful.

In terms of just one of the possibilities, the accidental or intentional administration, I would take it that in light of the magnitude of the number, whether you account for your multiplier or not, you would still posit as the most likely pattern administration very close to the time of arrest and/or death?

A. Yes.

Q. And, again, I take it raise the possibility of drug error with the administration of lasix?

A. Yes.

MR. STRATHY: I'm sorry, was that



J6 1
2 a yes?

3 THE WITNESS: Yes, with the
4 proviso that we still have to consider the other
5 alternatives.

6 Q. Yes, of course.

7 A. Including intentional
8 administration. Now, the one other thing in this
9 infant, and again we don't know what to make of
10 it, is that the baby had an extremely high post
mortem calcium. This was 34.5.

11 Q. Yes.

12 A. This is well outside the
13 normal range. I am assuming that very high
14 calcium resulted from administration of calcium
15 during resuscitation attempts. Calcium after
16 all if a very appropriate thing to try to use
17 during a resuscitation and in all likelihood it
18 does. I mention it primarily because it is an
19 outstanding and something of an outlandish number
20 compared to any of the other patients that we
21 have dealt with and I don't have a full
explanation for the extremely high calcium level.

22 Could this reflect again tissue
23 damage? It might, but I think we have to just
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J-7

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leave it at that.. It is a very high number.

Q. Do you in that same vein -
no pun intended, Doctor - attach any significance
to the potassium level of 7.3 recorded at 2:45
on the morning the child died?

A. Yes.

Q. That is an elevated
potassium level, is it not?

A. That is an elevated
potassium as well. That is an elevated potassium
as well. There again are many things that can
control potassium levels and that can cause
shifts in potassium concentrations. The
simplest acute shift that can occur in potassium
levels is changes in blood pH or acidity of the
blood. If a baby gets into a clinically bad
situation and, for example, is getting into
clinical trouble, is not as well oxygenated as
before, his blood acid begins increasing.

What happens in many circumstances
is that there is an exchange across a membrane of
a hydrogen ion from acid for potassium. There
is lots of potassium in the cells, very little
in the blood. Not quite as dramatic as the
difference with digoxin but a very large difference.



J-8

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So that exchange of a hydrogen ion for a potassium ion during an arrest would lead to an elevated potassium. We frequently see elevated potassium associated with extreme clinical situations where a baby is sick and acidotic.

A second possibility is:---

Q. Before we go on from that.

A. Yes, sure.

Q. pH recorded in the sample taken at the same time was 7.4. Can you tell me about that?

A. Well, I have another sample. I have a recording of 7.14.

Q. I'm sorry, 7.14?

A. That is very acidotic.

Q. Yes.

A. That is very acidotic.

Q. Well, it seems to me that we should link what you were saying to what is disclosed in the chart?

A. Yes, certainly, okay. We have a blood pH of 7.14.

Q. Yes.

A. So, under those clinical





1
2 circumstances I'm not surprised that the
3 potassium would rise.

4 The second possibility is tissue
5 injury as such. When cells die they release
6 potassium. Certainly we have evidence in this
7 child that cells are dying. The sub endocardial
8 changes, the papillary muscle necrosis.

9 Q. Yes.

10 A. And reasonably small amounts
11 of tissue dying can release significant amounts
12 of potassium. The third possibility is that
13 something has altered the sodium potassium ATPase.
14 This is the enzyme that maintains sodium outside,
15 potassium inside. The things that can do that
16 are decreasing oxygen, increasing acid, tissue
17 ischemia or fall in oxygen reaching the tissue,
18 fall in glucose reaching the tissue and finally
19 digoxin because digoxin by poisoning or
20 inhibiting, let's use that as a much better term,
21 I don't imply that in a sinister sense of poisoning,
22 but by inhibiting the sodium potassium pump
23 can lead to an increase in blood potassium as
24 one possible mechanism.

25 Now, in this child it is very hard
to separate out the relative roles of all of those things



1
2 because we know, first, that he is very
3 acidotic. So, that makes good sense on that
4 basis because that is probably the commonest
5 cause of acute shifts in potassium. We know that
6 he was receiving aldactazide which is a
7 diuretic which inhibits the kidney from excreting
8 potassium. So that if his blood potassium goes
9 up it is not as easy for him to excrete it. He
10 was on it for a very good clinical indication.

11 I'm not saying anything sinister there again,
12 but aldactazide will tend to retain potassium.

13 He was acidotic, he had tissue
14 that was dying and he had digoxin on board. So
15 that combination of each of these things led
16 to the potassium of 7.3, at best we can say
17 probably many of them contributed and what
18 relative role each of them played, I don't know.

19 Q. May we then begin a look
20 at Kevin Pacsai.

21 A. Okay.

22 Q. Who is the fourth of the
23 children whose chart you reviewed, Exhibit 106.

24 Again, Dr. Spielberg, a child on
25 digoxin therapy. The doctor's orders are found
at page 75 of the chart and the med chart is found



1

2

at page 80, or the med sheet is page 80. One
dose administered on the evening of March 11th.

3

4

A. Yes.

5

Q. The med sheet signed by
Nurse Nelles?

6

A. Yes.

7

Q. The order having been

8

written that day on the child's admission, a
dose of .02 milligrams twice a day based upon
what I now learn to call 5 micrograms?

10

A. Yes, a correct dose.

11

Q. Per kilogram. Yes. And

12

clearly a very troubled history prior to his
arrival at the Hospital for Sick Children?

13

14

A. Yes.

15

Q. He had rather severe problems

16

before getting even to McMaster and he came from
McMaster to your hospital?

17

A. Yes.

18

Q. At page 65 in the progress

19

notes, we read Nurse Nelles' note at 3:45 to six
o'clock in the morning. Of course, we have read
this and a number of other clinicians who have
been here and I know you have read it, Doctor.

20

21

22

23

A. Yes.

24

25



1
2 Q. Dr. Costigan comes and his
3 note is found on page 63. He records that he
4 was asked to see Kevin because of anxiety about
5 his - and I still can't read that word.

6 MR. ORTVED: Episodes.

7 MR. LAMEK: Q. Episodes of
8 bradycardia, thank you, down to 50 to 60,
9 alternating with rates of 150?

10 A. Yes.

11 Q. Dr. Costigan looked at the
12 rhythm strip, found a slightly prolonged PR
13 interval, sinus bradycardia, querying sinus or
14 nodal tachycardia?

15 A. Yes.

16 Q. With intermittent 2 to 1
17 heart block. His differential diagnosis was
18 sick sinus syndrome, possibly digoxin toxicity?

19 A. Yes.

20 Q. And he decided the child
21 should go to the ICU and he arranged for the
22 transfer and he ordered that digoxin be held?

23 A. Right.

24 Q. And his note upon the
25 child's admission to the ICU is found at page 66.
It records essentially the same history and makes



1
2 essentially the same differential diagnoses at
3 the bottom half of the page. His impression
4 is bradyarrhythmia secondary to either digoxin
5 toxicity or sinoatrial node disease, sick sinus
6 syndrome?

7 A. Yes.

8 Q. But he also records the
9 treatment that he and a fellow had given to
10 reduce the elevated potassium level in the child?

11 A. Yes.

12 Q. Kayexolate enema and so on?

13 A. Correct.

14 Q. And then the arrest note is
15 found at page 67. And that again we will not
16 take the time to read, we have all read it, and
17 you have I know.

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The question at the bottom of the page: How did the potassium get from 3.7 to 7.7 in less than 12 hours without any having been given was a question that has troubled Dr. Costigan, and he has been here and given evidence about it.

A. Certainly.

Q. And then it occurred to him the next day that perhaps he ought to check the digoxin level, and we have heard the history of how that was all done?

A. Yes.

Q. As far as the digoxin information is concerned, Dr. Spielberg, we have a measurement in an antemortem sample that was drawn in the ICU of greater than 10 nanograms per millilitre, not sufficient, unhappily, to do further dilution, although fairly it should be said that for whatever weight may be placed upon it, the computer in the biochemistry lab had made some projection and was suggesting that the ultimate level would be, what is it, 10.6?

A. Yes.

Q. Whether or not that has any reliability, goodness knows. All we know is more than 10 on a recorded basis.



1

2

A. Correct.

3

Q. And in the postmortem sample,

4

26 nanograms, postmortem sample drawn at autopsy.

5

There are levels recorded in fixed tissue, heart and

6

lung, and in unfixed, although frozen lung tissue

7

recorded at the Centre, which is 122 nanograms per
gram of digoxin?

8

A. Right.

9

Q. All right, Doctor, you

10

help me to understand what the significance of all
those numbers may be.

11

A. I will try. Kevin, and I

12

know, Mr. Commissioner, you will not like the word,

13

but probably is the most complicated of all the

14

children. We are unhappy with that fact as well

15

because we do not understand a great deal about him.

16

I will try my best to go through

17

what I think is relevant and see if we can come up

18

with any kind of understanding of what may or may not

19

have happened to this infant.

20

Q. Doctor, could I stop you

before you begin, I am sorry.

21

A. Sure.

22

MR. LAMEK: Mr. Commissioner, it is

23

5 minutes to one and I wonder, since Dr. Spielberg is

24

25



Spielberg, dr.ex.
(Lamek)

1

2

about to embark on this, whether it might be more
appropriate to come back a little early rather than
break this summary.

4

5

THE COMMISSIONER: For the first time
in my life I will be generous. We will not come back
until 2:30.

6

7

MR. LAMEK: More than I could have
asked for, sir.

8

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THE COMMISSIONER: An extra five
minutes and do not ever say I never gave you anything.

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---Luncheon adjournment.

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---Upon resuming at 2:30 p.m.

THE COMMISSIONER: Yes, Mr. Lamek?

MR. LAMEK: Mr. Commissioner, we were ---

THE COMMISSIONER: Just a moment,
please.

MR. LAMEK: Yes, I was just about to
say Mr. Roland has something that he wants to say.

MR. ROLAND: Mr. Commissioner, this
morning we dealt with a sample of something concerning
Kristin Inwood that was analyzed by Mr. Cimbura and
appears in his report. It appears in his report in
Exhibit 95C, that is his report dated March 25th,
1982 as Item 246 and is described by a Mr. Cimbura
as a small sample of brownish fluid in a vial, and
he gives the labelling for that as: Inwood, K.,
844-81, reported to be serum, and there was some
considerable discussion this morning of precisely
what that was. We have been able to determine that
from Virology and the Virology books the Hospital
over the lunch break, that that sample appears to
have been one taken at post mortem and at least in
the books, appears to be blood. I have extracted
or had extracted for me, pages 158 and 159 from the
virology book that indicates the same sample number
of 844, and that the sample was taken, as I have



1
2 indicated, of blood at the autopsy. I file that as
3 an exhibit.

4 THE COMMISSIONER: Yes.

5 THE REGISTRAR: 221.

6 THE COMMISSIONER: 221.

7 ---EXHIBIT NO. 221: Photocopy of pages 158 and
8 159 of the virology book.

9 THE COMMISSIONER: The fact that
10 it is blood and not serum, does that make any
11 difference to your evidence?

12 THE WITNESS: Blood, in a general
13 sense, will have a higher level than serum because
14 of the presence of red blood cells. The red cell
15 in children tends to have levels in the neighbourhood
16 on average of three times that in serum, and knowing
17 that it at least is a blood sample is helpful because
18 there was a question of whether it might have been
19 a tissue sample, which would have been totally
20 uninterpretable, so that this does help us somewhat
21 to at least rule out that it was a piece of tissue.

22 MR. LAMEK: Mr. Commissioner, I
23 am very grateful to Mr. Roland for that information,
24 and particularly to Dr. Ellis, who I understand
25 tracked it down over the course of the lunch break.

I point out that on the submission form



1
2 when that sample reached the Centre for Forensic
3 Sciences, it is described on the form as a small bottle
4 of serum with a number, from Baby Kristin Inwood.
5 Mr. Cimbura on his report I think was cautious enough
6 to say . it was a small bottle of brownish fluid
7 reported to be serum. That may at least have helped
8 to resolve some of the question about that sample.

9 Q. Perhaps we can go a little way
10 towards resolving some other questions about it,
11 Dr. Spielberg.

12 A. Yes.

13 Q. The final autopsy report in
14 the Inwood chart, and you do not need to look at this
15 unless you want to, identifies the prosector on
16 the autopsy as Dr. Taylor. We have heard from
17 Dr. Taylor, and Dr. Taylor, as I understood his
18 evidence, said that his normal practice when drawing
19 blood samples at autopsy was to take them from the
20 inferior vena cava.

21 Now, I cannot tell you whether he
22 followed his normal practice on this occasion, of
23 course, but if he did, then that would remove another
24 area of question about that Inwood sample, would it
25 not, the concerns that you had if it were drawn from
the heart?



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A. Yes, certainly if the sample were taken from the heart directly one would be concerned.

5

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Q. We are still left with the storage difficulties, of course?

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A. And if the myocardium was dying, it would have contributed to the overall circulatory digoxin as well, but certainly much less if it had been taken from inferior vena cava.

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THE COMMISSIONER: I wonder if I could just go back a bit. I have now looked at Exhibit 221. Mr. Roland, how does it tell us that it is blood?

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MR. ROLAND: Yes, I am sorry. If you look at the third item down, it is 884, Kristin Inwood, and this is, I gather, a book in which the pages are opened up and the matter is written across the entire page. So that if you turn the page to 159, the third item down, you will see blood, Pathology, Taylor, and it was taken for the purposes of testing for rubella and whatever those other two sets of letters indicate.

22

THE COMMISSIONER: Yes, all right.
Thank you.

23

24

25

MR. LAMEK: Q. We referred this



1
2 morning also, Dr. Spielberg, to the question of
3 the potassium levels in -- 7.3, who was that, that
4 was Inwood, was it not?

5 A. I have to go back and look in
6 honesty.

7 Q. Well, we are going to be
8 coming to the same thing with respect to Pacsai. I
9 will leave it until then.

10 A. Okay.

11 Q. You were about to tell us what
12 you thought was of significance in the Pacsai chart
13 and history?

14 A. Yes, sir.

15 Q. And help us to an understanding
16 of the significance of the digoxin data that we have
17 about that child. I wonder if you would do that,
18 please.

19 A. Okay. As I believe has
20 already been testified to, the child appears to
21 have had a disturbance of heart rhythm perhaps even
22 before he arrived at St. Joseph's in that there is
23 a note that his father had thought that he felt
24 that the child's heart was speeding up and slowing
25 down. So this may have well been a long standing
problem for Kevin.



1
2
3 In any case, he arrived at St. Joseph's
4 in very dire straits indeed. His body temperature
5 was 35.8. He had no detectable blood pressure. He
6 had a heart rate that at that time was 160, which is
7 more or less okay for a child his age, but we are
8 then told it sped up and slowed down and that he
9 was having major rhythm disturbances.

10 The other thing that was particularly
11 striking about this baby is that his blood pH or
12 the acid level in his blood, the acid level was
13 extremely high and the pH was very low, 6.79, in
14 fact, and that for three hours, as best as I can
15 determine it in St. Joseph's, they struggled to
16 correct the metabolic disturbances that the child
17 had and to treat what appeared to be an abnormally
18 rapid heart rate by giving him digoxin.

19 During this time his serum potassium
20 in fact was rather high during most of his stay at
21 St. Joseph's, albeit that he was quite acidotic
22 at that time, and as we said, acidosis can elevate
23 a serum potassium level. It is striking that his
24 pH remained even at a half hour past midnight or
25 25 minutes past midnight and he had arrived at 21:35.
His pH was still 7.07, so that this child, in fact,
had a very long difficult time when his body was



1
2 deprived of all the natural things that will be going
3 on, including having an extremely low blood sugar,
4 low oxygen, marked acidosis.

5 So here we have a child who, in many
6 ways, it would have been surprising that he survived
7 that episode and the attempts made at the Hospital
8 obviously were sufficient to keep him alive until
9 the time he could be transferred to McMaster.

10 Also of note at that time is that he
11 had a coagulation problem. His prothrombin time was
12 more than twice normal. We never have a good
13 explanation for this. It might reflect damage to
14 the liver, possibly on the basis of the fact that
15 profusion of the liver during this whole period of
16 time might have been abnormal. We do not have a
17 good explanation.

18 In any case, he arrives at McMaster,
19 having had this really tremendously prolonged, and
20 by anyone's criteria in clinical pediatrics,
21 tremendous prolonged time when he was extremely,
22 extremely sick. Digoxin was continued at that point,
23 although doses were adjusted in the hospital at
24 McMaster. He had one digoxin level of 1.8 nanograms
25 per ml, which I believe was on the 9th, which was
two days prior to his transfer, and we have no



1
2 subsequent digoxin levels on the child from the 9th
3 until the time he was transferred.

4 Should we consider two possibilities?
5 I think we should at least consider them. I doubt
6 if they are relevant. Perhaps the 1.8 was an error
7 or perhaps he received excessive doses of digoxin at
8 McMaster prior to the time of his transfer. We have
9 no evidence for this or against this. I think it
unlikely.

10 Q. I would have thought if the
11 second were the case, the first would of necessity
12 have to be the case?

13 A. Yes.

14 Q. Yes.

15 A. Now, things were not quite
16 right with this child at McMaster. That is why he
17 was transferred. The transfer note indicates a
18 major concern about bradycardia, for indeed the
19 child's heart rate was still slower than it should
20 have been for his age. Was this related to digoxin;
21 was this related to this child's primary disease,
22 for we already know that he had a rhythm disturbance,
23 I cannot say. In any case, he is transferred.
24 Interestingly, while at McMaster and upon his transfer,
25 despite the fact that his blood pH is corrected, and



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3 in fact over-corrected and now he has an alkaline
4 blood pH, his potassium is still high normal, in the
5 4.5, 4.6 range, that neighbourhood, which again is
6 a bit surprising because I would have expected his
7 potassium to be lower if he was indeed alkalotic,
8 since again potassium moves into cells in the face
9 of alkalosis.

10 All of these metabolic kinds of things
11 that were going on, the profundity of the acidosis
12 and the ion shifts that appear to be going on raise
13 the question of some process going on in this child
14 of a metabolic nature, perhaps involving potassium,
15 perhaps involving acidosis. We cannot really deter-
16 mine that, however. The suggestion is there and
17 the concern is there, particularly since he continues
18 to have a rhythm disturbance which could be intrinsic
19 to his heart or could be related to a metabolic
20 disturbance.

21 In any case, he arrives here with
22 persisting rhythm problems. His heart is still a
23 little slow, too slow for age and we do not have an
24 adequate explanation of what happens for him. When
25 he arrives, his liver is felt 3 centimetres below the
costal margin. That is a little bit large. We are
not told what the liver span is, which will be able



1
2 to tell us whether it is a big liver as a result
3 perhaps of some degree of heart failure or from
4 some other process. It is of some concern to us
5 in any case.

6 Now, my understanding, again, is that
7 the rhythm disturbance became progressively worse
8 at the time that he was admitted to 4A/B, and
9 eventually became sufficiently slow and irregular
10 with heart rate going down as low as 60 that the
11 decision was made after doing electrocardiograms
12 and examining the child that there was a good deal
13 of concern about him, and he was transferred to the
14 ICU, with the question raised might this be digoxin
15 toxicity, might this be "sick sinus syndrome", which
16 is again a rhythm disturbance which might have
17 explained everything that had occurred prior.

18 He is transferred to the ICU. Now,
19 my understanding is that the level obtained, the
20 greater than 10, was shortly after his transfer to
21 the ICU. This was not a sample specifically drawn
22 for digoxin. It was drawn for another purpose, and
23 the blood was analyzed and found to be greater than
24 10 with the suggestion that it was in the 10 range
25 from the assay, albeit greater than 10. He then
continued in the ICU, and several things are striking



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about his ICU course, including the fact that the
baby returned to sinus rhythm while in the ICU.
So that for a period of time, the baby's heart rate
and his rhythm was normal. Despite the fact that we
have a reading of 10 or greater in his serum at the
time he was transferred to the ICU, his heart rate
and rhythm for a period of time was entirely normal.



RCSCH

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This is a bit unusual and we will have to come back to it, because I don't have a very good explanation for it, but it is something we are going to have to deal with. Because in the face of that elevated digoxin level apparently, and his pre-existing heart disease, which must have been profound given the situation in which the baby found himself earlier at St. Joseph's, nonetheless in the face of both his heart disease and what appears to be an elevated digoxin level he establishes a normal sinus rhythm.

Then rhythm disturbances reoccur, he becomes apneic, bradycardic, arrests, again a prolonged resuscitation effort is made and the baby, including the placement of transthoracic pacemaker wires, and he goes on to die.

Also noted at that time, as you said, was an elevated potassium level while in the ICU of approximately 7.7 on a non-hemolyzed sample, the first sample I think we can discount because it was hemolyzed and that will confuse a potassium level.

At post mortem we are told that



BB-2

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we end up with a blood level of 26.

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What can we say about the course
of this baby; and what can we say about the
digoxin levels?

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Well, in the first instance it
strikes me as the 10 and the 26, or greater than
10 and 26 are actually rather consistent with
each other. Here we have a situation where we
have a pre-mortem level, not an exact level, but
a pre-mortem level and a post mortem level that
fits in with our general concept of what might
happen between a pre and post mortem level. In
other words a rise of two to threefold. This
seems reasonably appropriate.

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Then we have to go back and ask,
how could Kevin have ended up having this kind of
level?

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18

THE COMMISSIONER: Excuse me,
Doctor.

19

20

21

THE WITNESS: Yes.

THE COMMISSIONER: Is this greater
than 10 being the 10 range, did you get that from
Dr. Ellis' book?

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THE WITNESS: Yes I believe it was
testified to in the preliminary hearing from Dr.



BB-3

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Ellis' book.

THE COMMISSIONER: 10.7?

MR. LAMEK: I think it projected
10.6.

THE WITNESS: The estimated 10.6.

MR. LAMEK: Q. But the recorded
level as opposed to the projected level was
merely greater than 10?

A. Yes.

THE COMMISSIONER: I think Dr.
Ellis said the closer it is to that, what is
that exhibit? Anyway, you are assuming that it
is just slightly greater than 10, is that right?

THE WITNESS: Or in that range,
yes. Obviously we can't know for sure. The
projection was 10.6, that is usually based on,
we run a standard curve up to a certain point.
You don't have enough sample to dilute that
down to be sure, the counts you get back from
the IRA are reasonably close to that value and
you make an educated guess, but really end up
reporting greater than 10, because that is the
upper limit of your assurance with that sample.

In any case the ten or greater
than ten and 26 seem reasonably consistent. In



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fact if it had been 15 and the post mortem 26 that would have been consistent. In fact had it been pre-mortem in the twenties and post mortem 26 again we have reasonably consistent numbers, and this is different again than some of the other children that we have been dealing with and in whom we don't have these kinds of pre-mortem data.

What might this mean? Well there again are several possibilities. One is that the infant would have been given some digoxin to elevate his serum concentration to ten or greater. Now presumably this - I am not sure exactly what time the blood sample was obtained in the ICU relative to the time of transfer, but presumably this would have been before transfer to the ICU, we can't be one hundred per cent sure of that but it seems reasonable.

Q. I believe this was in the ICU shortly after the transfer to the ICU?

A. That the sample was taken?

Q. Yes.

A. Yes. I think it is reasonable to suspect that if the child had received digoxin, that in fact it would have been



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given perhaps shortly before he left for ~~6~~ A/B,
again timing would become very difficult indeed.

Now we are dealing though with
the situation where it is very hard to predict
what was going on in the ICU during that time.
If in fact the ten is a stable level, or a steady
state level, and then went up to 26, well that
suggests that it might have been considerably
before he left the ward, which opens a wider
time frame. If in fact it had been a distribution
phase, the alpha phase that we are talking about,
one might well have suspected that the level would
have fallen in the ICU after transfer. Again
assuming that he had been given some digoxin on
4A/B and that the level had then fallen in the
ICU, he was in the ICU about four hours I
believe, that is a reasonably long period of time
and one would have expected further distribution
of the drug if he were in an alpha phase, again
because it comes down with the half life of about
30 minutes.

This was a real quandary for us,
because we end up then with a post mortem value of
26 which is really more consistent with the value
having been high at a steady state level and high



BB-6

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2 at the time that the baby died and we are left
3 with the further enigma that he re-establish
4 sinus rhythm in the ICU, despite what appears to
5 be an elevated digoxin level, and in the face of
6 a pre-existing cardiac arrhythmia.

7 Q. Well I think probably a
8 year ago the only two possible explanations we
9 would have had for Kevin's problem would have
10 been administration of digoxin in some way or
11 another, with an amount calculated to produce
12 his level of ten, or perhaps a little bit greater,
13 going up to 26 post mortem. But there have been
14 certain things that have occurred over the last
15 year, both in the published literature, as well
16 as at least one infant who already has been the
17 subject of an inquest, and several other
18 infants who have been followed on the cardiology
19 floors on 4A/B, where blood levels have exhibited
20 what we will call ^{re-} ~~p~~ distribution phenomena, which
21 is one thing that I think we have to accept as
22 one potential explanation of what happened to
23 Kevin.
24

25 Now under circumstances such as
a level of ten, a year ago we might have thought
that this could never happen in a living patient,



BB-7

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2 and in fact we have seen it now in several
3 patients, where a level despite no excessive
4 administration of digoxin, for reasons which in
5 some patients in the literature have been
6 explained on the basis of renal failure, and
7 other patients have been explained on the basis of
8 tissue damage, to a variety of different organs
9 in a variety of different ways. Unfortunately
10 with so many variables that we can't always define
11 them, but patients whose serum digoxin levels have
12 continued to rise to levels in fact very much in
13 the range of ten during life despite no
14 administration of digoxin.

15 Now the question - that does not
16 mean they didn't have digoxin in the first place,
17 this is presupposing that the infants indeed had
18 digoxin in their bodies but that a small fraction
19 was lost during life. What does this mean in
20 terms of Kevin Pacsai? The enigma we face is the
21 fact he re-established sinus rhythm in the face of
22 an apparently elevated digoxin level and the
23 rhythm disturbance, and in fact lived four hours.

24 Q. I am sorry, you say four
25 hours, forgive me for interrupting you.

A. Yes, certainly.



BB-8

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Q. Are you looking at something in the chart in arriving at that four hours? My recollection of the evidence and my reading of the chart is that he went to the ICU at about six o'clock?

A. Yes.

Q. And his arrest at 8:45. He was pronounced dead at ten o'clock, but his arrest was at 8:45?

A. Okay.

Q. So if four hours is any magic in this discussion I am not sure we should be addressing it?

A. Oh no, no. I am saying not matters of minutes, rather matters of hours.

Q. Yes.

A. Certainly from the period of six to at least his arrest and then subsequently.

Now struggling with those numbers, I don't have a good explanation. I believe the possibility still exists that the child could have been given an excessive dose of digoxin, much smaller quantities of course than these other babies, because the levels are much lower, we don't have to back calculate them you can just



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calculate from, you know 10 or 20 versus the 70
or 80; could have received an excessive dose
of digoxin on the ward prior to transfer.

I think the other possibility has
to be considered, that in light of other babies
that we have now seen, as well as the published
literature that increases in serum digoxin level
from tissue loss may have occurred in this baby,
thus the baby serum concentration would have been
increased, but the concentration at his myocardium
might not have been increased, and in fact might
have been slightly decreased. Because again to
go to a level of 10 or 20 from a level of 1.8 is
a very tiny fraction of loss of digoxin as we
discussed yesterday. We are not talking about
massive digoxin release, we are talking about
probably two per cent, maybe three per cent, very,
very small amount of release, from mechanisms that
again in honesty we don't understand, except that
we have seen it in other patients.

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Thus we have a situation where
the baby's total body digoxin was the same, but
where his serum level in fact was higher. Under
those circumstances I find it easier to imagine
the child going back into sinus rhythm. The fact



BB-10

1
2 that he then reverted to an abnormal rhythm is
3 basically what had been happening to the child
4 all along. In fact the child had tremendous
5 rhythm disturbance and was going up and down,
6 and up and down, and that he finally died from a
7 rhythm disturbance is not surprising.

8 Thus I think the three
9 possibilities that exist in the infant, that I
10 have to at least consider pharmacologically is:
11 one, accidental or intentional administration of
12 digoxin; and two, abnormal pathophysiology with
13 a rising serum digoxin level as a result of
14 phenomena that again we do not understand, but
15 that in fact we see.

16 Q. As between those
17 possibilities ---

18 Q. I'm sorry, you said there
19 were three.

20 THE WITNESS: Accidental;
21 intentional or abnormal pathophysiology.

22 Now with respect to the serum
23 potassium level, I am sorry, because you asked me
24 about that before. Again we talked about some
25 of the ways that serum potassium levels can go up,
one of them was acidosis. Now the child at the



BB-11

1 time of transfer was not particularly acidotic
2 and as such I don't think we can rationally
3 invoke acidosis at the time of transfer as an
4 explanation for the elevated potassium level.
5 One of them was tissue hypoxia or tissue damage.

6 Now we don't have hard evidence
7 again, there doesn't appear to be a large, for
8 instance dead area of heart muscle in this baby
9 at autopsy. So we don't have evidence for
10 that phenomena, so we can't directly invoke that.
11 We can potentially invoke some sort of
12 abnormality in sodium potassium ATPase, either
13 on the basis of the patient's disease process,
14 which may have been responsible for his
15 potassium problems earlier on and his arrhythmias
16 and what happened subsequently. Or we can
17 invoke digoxin toxicity, since digoxin toxicity
18 can be associated with that.

19 Now, you will excuse me for just
20 one second, I have to look up one thing in the
21 chart which I didn't record accurately in my
22 notes, I just put an arrow and I want a number.
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BM/PS

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It doesn't all that much

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in fact. The issue was whether the serum calcium level was dramatically abnormal one way or the other and it is not in him. So, this really does not help us.

6

Q. Yes.

7

A. Thus, it might be, and again

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having seen some of these things happening in the

9

last year as well as reading about them in the

10

literature, that whatever process, pathophysiologic

11

process might cause release of digoxin influencing

12

the sodium potassium ATPase might also have in

13

the process influenced potassium transport

14

again because of an abnormality in the sodium

15

potassium ATPase, which is again what digoxin

16

binds to and what is at least possible in this

infant that went wrong.

17

Q. Dr. Spielberg, can you help

18

me with one thing. You have referred to the re-

19

establishment of normal sinus rhythm in Kevin

Pacsai in the ICU.

20

A. Yes.

21

Q. Can you help me find that in

22

the chart, if you will?

23

A. Yes. I will have to flip through

24

25



1
2 it again. It is in the typed summary.

3 Q. Yes.

4 A. And I am sorry, I don't
5 remember the page. Page 101, Dr. Michael
6 Schaffer, fellow in Cardiology's discharge
7 summary:

8 "During the evening of admission the
9 child became bardycardic, 2 to 1,
10 3 to 1, atrial ventricular block
11 and was transferred to the Intensive
12 Care Unit. In the Intensive Care
13 Unit the child was noted to be back in
14 sinus rhythm. The potassium was
15 recorded to be 9..."

16 And as we said this was a hemolyzed sample.

17 "...and was repeated and repeat
18 value was 7.7."

19 And at that time the various interventions which
20 you had mentioned took place, including glucose
21 infusions, bicarbonate infusions and Kayexolate
22 in an attempt to lower the child's serum potas-
23 sium.

24 Q. Okay.

25 Thank you for that. It is in the
discharge report.



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A. Yes.

Q. Were you able to find any
reference to it in the chart itself?

A. I could not find the EKG's, no,
relative to that.

Q. Or even any notation in the
chart from the ICU as to what was going on with
the child.

A. I did not notice it when I
read through initially, no.

Q. I am certainly prepared that Dr.
Schaffer didn't make all that up.

A. No, certainly no.

Q. But I would like to know the
source of his information because, like you, I find
nothing in the chart to suggest it.

A. No. As I remember reading
through, and again I would have to read it through
in detail to be absolutely sure, and some of it,
the xerography was rather difficult to read, I don't,
no, notice a specific note. Most of the notes in the
chart were summary statements of interventions,
the transfer note, the statements about blood gases
and then subsequently the nursing notes on Page
65.

Q. Yes.



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3 A. Just prior to transfer and then
4 really very little in the ICU. The only ICU note is
5 really Dr. Costigan's final note here as far as I
6 can tell.

7 Q. That is Page 66 of the chart.

8 A. Page 66, excuse me, yes.

9 Q. Yes. You see, that is what
10 puzzles me because, as I read that, in the middle
11 of this page underneath Transfer to ICU, Costigan
12 is noted and he has told us that he took the child
13 to the ICU.

14 A. Yes.

15 Q. "On leaving the ward developed
16 bradycardia to 40, cyanosis and
17 brief apnea, responded to stimulation.
18 In ICU further episodes of bradycardia
19 with 3 to 4 block." "

20 A. These certainly occurred at
21 some time.

22 Q. Yes. I don't see anything in
23 that note about restoration of normal sinus
24 rhythm.

25 A. Yes. I suppose the real
question is, and I questioned it as well, you know,
if I had to reconstruct what was going on over that



1
2 period of time, remember, we are talking hours and
3 not minutes in the ICU.

4 Q. Yes.

5 A. As best I could try to put
6 things together it appears as though he stabilized
7 initially in the ICU, for if he was running brady-
8 cardia down to 40 that entire period of three hours,
9 or whatever, he would not have survived.

10 Q. This is quite significant, I
11 think.

12 A. Yes.

13 I don't find it unusual that in
14 Dr. Costigan's note he wouldn't have mentioned,
15 you know, up and down episodes during that period of
16 time. I don't know if we have anything else that
17 can help us in that regard.

18 MR. BROWN: Excuse me, Mr. Commissioner.
19 If I could perhaps direct you to Page 69, the bottom
20 of this page there appears to be a note by Dr.
21 Schaffe-.

22 MR. LAMEK: Yes, there does. I noted
23 that one but I would have thought -- there is a
24 reference there to the ---

25 A. ECG sinus rhythm acts as
90.

Q. Yes, but that I would have
thought refers to an earlier part of the day, does it,



1
2 because then it goes on:

3 "During the evening. Subsequently
4 the patient..."

5 A. What date is this?

6 3/12, 10 A.M.

7 Q. Yes.

8 A. Something 10:30 a.m.

9 Q. Yes.

10 MR. BROWN: But there does appear to
11 be a reference to the transfer to the ICU, fourth
12 to bottom line.

13 THE WITNESS: Yes.

14 MR. LAMEK: Q. Yes, it does, but that
15 follows the reference to the ECG with the sinus
16 rhythm because, as I understand you, the re-
17 establishment of normal sinus rhythm in the ICU
18 is a matter to which you attach considerable
19 importance.

20 A. I believe so because it makes
21 the assumption that the ten at a reasonably steady
22 concentration would have reflected exogenous
23 administration of a large amount that then would
24 have to come down to that less likely than the idea
25 that some of it may have been distributed. I believe
it is an important point. I am not sure how we can



1
2 get at it further except perhaps by taking with the
3 people involved.

4 Q. Yes.

5 A. I think that would be helpful.

6 MR. ROLAND: If you look at the bottom
7 of Page 69 there is an addendum reference to regular
8 sinus rhythm. It is hard to read but appears on the
9 last three lines to be .06 nanograms of atropine
10 caused the patient to (something) his heart rate
to regular sinus rhythm.

11 Q. Oh, yes, yes.

12 A. Yes. I don't know.

13 MR. ROLAND: Maybe the original could
14 tell us that.

15 MR. LAMEK: Q. That is Dr. Schaffer
note as well?

16 A. Yes.

17 MR. ROLAND: And that is after the
18 transfer to the ICU?

19 MR. LAMEK: Apparently, yes.

20 A. Yes.

21 Q. Okay.

22 A. So, I can't resolve that my-
23 self.

24 Q. No, I was puzzled with that.
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A. No, I was myself as well and I kept searching. I think the issue though is a very real one. The other thing is that, and the initial concern was, after all, here is an infant who had a very severe rhythm disturbance, as has been already documented as a severe rhythm disturbance, as has already been documented at other hospitals and at Sick Kids who was on digoxin and did manage to survive in the ICU for a rather long period of time and if again this represented a steady state level, which seems more likely, be it dedistribution or redistribution, because the post-mortem level is more consistent with that, it becomes difficult to imagine a scenario, although still possible and I still cannot rule it out, that that represented exogenous administration in that the child survived that long with a level that high in the ICU.

Q. Okay. In that regard, two matters, Dr. Spielberg. Do you attach any significance to the fact that notwithstanding the history of rhythm disturbance, the child had a structurally normal heart, an anatomically undiseased heart?

A. Yes, yes.

Q. Would that enable him perhaps to withstand the beginnings of intoxication more



1
2 successfully than children with diseased or defective
3 hearts?

4 A. Probably not in that he had
5 a primary rhythm disturbance which might have two
6 possible causes. Not an anatomical abnormality but
7 an abnormality in the conducting system.

8 Q. Yes.

9 A. And in a general sense, as we
10 said yesterday, patients with conducting system
11 abnormalities might well have increased problems
12 with digoxin.

13 The second issue being that if he had
14 a metabolic disturbance, which might have explained
15 part of the potassium problems and the acidosis
16 problem and the digoxin problems, again, this
17 might further predispose in that anything, any
18 process, you know, that we could postulate, that
19 would alter this pump mechanism would make, again,
20 somebody more susceptible rather than less susceptible
21 to digoxin toxicity.

22 Q. Well, let's pursue that. Let's
23 take those things in isolation for the moment.
24 Other things being equal, is a child with an
25 anatomically normal heart in a better position to
resist the toxic effects of digoxin at levels like



1
2 ten in the blood than is a child with a diseased or
3 structurally abnormal heart?

4 A. Yes, as long as he does not have
5 an abnormality.

6 Q. Okay, if everything being equal,
7 let's leave that aside for the moment.

8 A. Yes.

9 Q. Now, you say offsetting
10 that, however, are a couple of considerations:

11 "(1) This child has a history of
12 dysrhythmia. He may have some problem
13 with the electrical conducting system in
14 the heart and that would predispose him
15 to toxicity and the manifestation of
16 toxic effects from digoxin and, also,
17 there may be some electrolyte
18 problem with this child, which again
19 would tend to cancel out any advantage
20 he might have from his structural
21 abnormality."

22 A. It could, conceivably, yes.

23 Q. All right, it could. But,
24 Doctor, we are talking about levels of ten for this
25 stage or something above ten.

A. Yes.



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Q. And we know that patients have survived with it.

A. Yes.

Q. That sort of level in the blood.

A. Yes.

Q. We know, for example, that Estrella, whom we are coming to, had a level of 9.4 in the blood on January 7th, 1981 and she survived that.

A. Yes, that is correct.

Q. What if the ten level recorded in the sample drawn at approximately 6:30 in the morning, in the case of Pacsai, subsequently increased and that toxic effects were being felt by that child prior to 6:30, subsequent to 6:30, but the distribution continued to the point where the toxic effects overtook him. Is that a possible scenario?

A. I'm not quite sure I understand. In other words, postulating that the level is now rising?

Q. Yes.

A. In some manner. Again, I would be very surprised if he could have been converted back into sinus rhythm under those



1
2 circumstances with a rising level from exogenous
3 administration. If it were coming out of tissue ---

4 Q. Now, when I say a rising
5 level, I mean a rising level, continued distribution
6 and therefore an increasing level of tissue. The
7 blood rate dropping, in other words.

8 A. In other words, the blood
9 dropping, okay.

10 Q. I'm sorry, my confusion.

11 A. I'm sorry.

12 Q. My confusion. Blood rate drop-
13 ping, continued distribution.

14 A. That is conceivable. So,
15 in other words, we would be talking about an alpha
16 phase.

17 Q. Yes.

18 A. We would be somewhere on that.

19 Q. Yes, ten still in the alpha
20 phase.

21 A. Yes.

22 Q. Would the possibility of that
23 or the probability of that reflect the mode of
24 administration had there been an administration of
25 digoxin? Would it make any difference how that dose



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was administered?

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A. In terms of route or...?

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Q. Yes, in terms of route.

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A. Again, conceivably given the different types of curves that we had talked about before.

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Q. Yes.

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A. In that the oral administration curve gives a rather different profile than an intravenous distribution curve.

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Q. Had the child received a dose of digoxin orally shortly before leaving the ward would distribution still have been continuing throughout the 2-1/2 hours that he was in the ward, or 2-3/4 hours, three hours in the ICU before arrest?

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A. Hard to predict for certain. If we are talking about an oral dose administered. ---

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Q. Well, it might be helpful.

Other counsel may be interested in it, Dr. Spielberg.

Are you aware that a sample of Pacsai's postmortem blood was sent to the Mount Sinai Hospital for analysis?

A. I was not aware of that.

Q. I understand the evidence has been, and there will be evidence to make this plain, that the level reported from Mount Sinai Hospital after assay of Pacsai's postmortem blood was 112 nanograms per millilitre. Now, I ask you to accept for the moment that that be the level, and I do not know what you know about the assay techniques and procedures at Mount Sinai, do you have any comment on that as a reported level from that hospital?

A. Five full differences and determination on the same sample leaves one a bit disturbed, I suppose. Again, we could use 112 as a number and go through reanalysis. I would not know what to make of it, again particularly in the clinical setting of the patient and his survival on the ward. If we were talking about him being on the ward for at least several hours, we then have to be talking about reasonably steady state concentrations.



DD2

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3 As such, we would have to be talking about levels
4 in life somewhere between 40 and 60, and having
5 survived that with re-establishment of sinus rhythm
6 in the face of a heart with a rhythm disturbance for
7 two or three hours on the ward, in response to your
8 question it does not fit very well pharmacologically
9 with anything.

10 Q. You, as a pharmacologist
11 putting that together with the other data, would
12 regard it as anomalous certainly?

13 A. I would have to think that
14 something is very strange about the sample. It does
15 not fit well either with the child's clinical course
16 or with a variety of different types of putting things
17 together because, again, we have to remember that
18 this child lived a long time, unless he received
19 the dose in the ICU. The only way that number becomes
20 reasonable is if he received an acute dose very close
21 to the time of death in the ICU.

22 Q. But even then, you would
23 have difficulty of reconciling the two results
24 from the two hospitals in the postmortem samples?

25 A. I would have, yes.

Q. You have said that the greater



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than 10 and the 25, 26 numbers tend to be corroborative of each other?

A. They appear to fit reasonably well.

Q. Doctor, of the three possibilities that you identified to explain the Pacsai situation, is there one for which you have a preference on the basis of your expertise?

A. Again if I had had to be asked the same question a year ago ---

Q. Well, I am asking you now.

A. --- I would have said administration. Today, with everything that we have known about the increasing knowledge of the pathophysiology of digoxin, I believe the most reasonable explanation I have for this child is the third, an abnormal pathophysiology which led to loss of digoxin from the child's tissue in small quantities, leading to an elevation in his level.

Q. I trust you will flatter me at least to this extent of reserving your final judgment on choice until you have considered the scenario I put to you; will you do that?

A. Certainly.

Q. We come, then, to the last



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of the children whose charts you reviewed, and that is Janice Estrella. Now, Dr. Spielberg, I do not know to what extent you have read or have been made acquainted with the evidence that we have heard in this Commission, I tell you we have heard a very great deal of evidence in dispute about the wholesomeness of the gutter blood sample or lack of wholesomeness, and therefore, the reliability of the level found in it.

I say to you, please, unless you have something substantially new to add to this dispute, I do not propose to get you into that area. By all means if you think there is something useful to be added, we would be delighted to hear from you.

A. Certainly. There may be as we get into the discussion.

Q. With Estrella, of course, this is a situation of a child who had had digoxin withheld for four days preceding her death, following a recorded level of greater than 5 or 4.7, whatever the top of the calibration scale was on January the 7th.

A. Yes.

Q. We know from a review of the digoxin books kept by Dr. Ellis that that number was



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in fact 9.4.

A. Yes.

Q. Digoxin was held, and in subsequent days the level dropped to, again, greater than 4.7, which as I recall it, was established at 7.8. Then a day where there was insufficient quantity to get a level, and then 4.7 -- not greater than, but apparently on the nose.

Then she died, and although the evidence has been a little confused and contradictory about how it came about, a postmortem sample of blood was ordered to be drawn at autopsy for digoxin assay. You are familiar with the story as to how that instruction was overlooked by the pathology resident doing the autopsy and how he went back for it later and the manner in which he obtained it.

A. Yes.

Q. He obtained two samples, as you know: one from the severed iliac vein, into which he inserted the end of a syringe while someone else massaged the leg, and the other from the pelvic cavity.

A. Yes.

Q. And those two samples were submitted to biochemistry, as you know, and the



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levels recorded in them were respectively 72 nanograms in the pelvic gutter sample, and greater than 4.7 in the leg vein sample, there not being sufficient quantity of the latter to make further dilutions.

A. Yes.

Q. And eventually, that information wound its way back to the ward, arriving there some time in the second week in March and assumed a significance in the minds of those on the ward the following week when the Pacsai numbers came to their attention. You are familiar with that history?

A. Yes.

Q. As far as other digoxin data are concerned, there really is nothing of any reliable nature from any other testing or sampling that has been done, so far as I am aware, and therefore, we are left with those two numbers: 72 and greater than 4.7. Can you be of assistance to us, please, in the understanding of those numbers and their significance, if any, in understanding the death of Janice Estrella? Once again, I have asked you that question and invited you to make a long speech just at the time when we normally break. My timing is impeccable, Mr. Commissioner. Rather than interrupt you, I think we would rather come back.



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THE COMMISSIONER: Yes, all right,
we will take 15 minutes then.

MR. LAMEK: Thank you.

---Short recess.

---Upon resuming.

THE COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Thank you, sir.

Q. Dr. Spielberg, just as we
broke, I asked you the question and we are ready for
the answer. What can you do to help us about your
understanding of the Estrella case in the light of
the recorded digoxin levels?

A. As again I gather has already
been testified to, this little girl was four months
old and had Down's Syndrome with trisomy 21,
and was admitted because of really severe failure
to thrive. She had not gained any weight in nine
weeks which, in a pediatric sense in a child this
age is a severe problem. There is also the -- then
she was admitted and I gather had some attempt made
at surgical correction of some of her problems.

The real issues relate to what can we
do with the digoxin numbers which we have available
for her, and basically, we have several, as you
suggest, which are pre-mortem and which were elevated



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2 at a time that her blood urea nitrogen was also
3 somewhat elevated, you know, at that particular time.
4 Because of the elevation, the initial rise in her
5 digoxin concentrations, it was felt that yes indeed
6 they should withhold all further digoxin and allow
7 the levels to return back to normal.

8 Now with the values that we have,
9 which were in the 9.4, 7.8 and 4.7 range, if we
10 make the following assumption that no digoxin was
11 administered to the baby during this time and that
12 no tissue loss occurred during this time so that
13 the rate of decline in the blood level reflects her
14 rate of excretion of the drug, we can make a guesti-
15 mate of half life, and the reason that we want to
16 do this, and this is a beta excretion half life,

17 the reason that we would want to do this is
18 that we would want to estimate in a rough manner
19 what her blood level might have been at the time
20 of death because we do not have a level at the time
21 of death or even the day before that.

22 Now, in order to do that what we do
23 is we look at the numbers 9.4 and 7.8 and 4.7 and
24 we can either plot it on a semi-logarithmic plot or
25 do another first order kinetic analysis, and we come
out with a half life somewhere in the range of 48 to



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2 52 hours, a reasonably long half life but not all
3 that abnormal for a child in this clinical situation
4 where at one point she did have an elevated BUN or
5 blood urea nitrogen, which stayed up somewhat and
6 then began to return towards normal.

7 Q. Did you arrive at that by
8 calculation, Dr. Spielberg?

9 A. The estimate of half life.

10 Q. Yes, do you arrive at that
11 by calculation?

12 A. I arrived at it by doing a
13 semi-logarithmic plot, which means to take the
14 numbers on semi-logarithmic paper and try to estimate
15 a reasonable line through the three points,
16 recognizing that there can be a lot of fluctuation,
17 and in fact, these three points do not lie on a
18 straight line, as you can see here. We make a
19 rough guesstimate and it is, at best a rough guesstimate.

20 From that we try to say what kind of
21 blood level, assuming that the digoxin continued down
22 at the same rate -- it is an assumption -- what level
23 might she have achieved at approximately the time of
24 death or shortly before the time of death. And as
25 best I can estimate, and again it is rough because
we only have three points, the level around the time



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2 of death, assuming no more administration, would
3 have been somewhere between 2 and 3 nanograms per ml.
4 Again, I emphasize the assumptions and that it is
5 rough, but that will be about 2 to 3 nanograms per ml.

6 Now, under those circumstances, if we
7 have to deal with the first postmortem number which
8 was greater than 4.7, if we deal with a range of
9 multiplier factors, if you will, of 2 to 3-fold,
10 then if her level was as low as 2 and it went up 2-
11 fold, we would expect a postmortem level of about 4;
12 if her level was 3 with a multiplier factor of 3,
13 we would get a level of 9; and if we are off even a
14 little bit in our calculations, again, the range
could be broader.

15 As such, a level greater than 4.7 is
16 not really very unexpected. In fact, I would have
17 expected just on the basis of where the child's
18 digoxin level would have been, assuming that excretion
19 was the same, to be 4.7 or greater on the average.
20 That is about as far as we can take that part of
21 the analysis because, again, we do not have other
points closer to the time of death.

22 So am I surprised by greater than 4.7,
23 no, in fact, I would have expected greater than 4.7
24 if nothing else happened to the baby.
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RCHSC 1

EE-1 2

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Q. Yes.

A. Now we have to deal with

72, this is a very different story obviously.

Of course again it remained a very concerning

matter. We have to go through our basic

hypotheses as to how the 72 could have occurred.

The two hypotheses which we

always have to accept is intentional administration

of an overdose of digoxin; and accidental

administration of a dose of digoxin, large or

small.

Q. Are these on the

assumption that 72 is a real number?

A. These are on the assumption

that the 72 is a real number, that is right, then

we will have to deal with, is it a real number?

Now again we will assume 72, and

that there has been no post mortem change and in

fact that reflects pre-mortem and we come up again

with the range of possibilities from acute as

soon as circulation stopped as low as 8 micrograms,

to this central volume which we have talked about

which seems a bit more reasonable, which is about

200 micrograms, again less than one adult vial

but more than one pediatric vial, it is about



EE-2

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2 less than half of an adult vial. Then the
3 steady state circumstance again, assuming 15
4 litres per kilogram, 3.2 milograms or the
5 equivalent of somewhere over six adult vials or
6 60 pediatric vials.

7 Now, we have to take the
8 standard types of multipliers into account, and
9 we will take a threefold increase which would
10 mean that her actual blood level, assuming that
11 the 72 post mortem is a correct value, and that
12 the pre-mortem now is three times less, than the
13 72, then we have to divide each of those by three
14 of course and you would get, for this acute
15 situation at termination of circulation, two
16 micrograms or two point something micrograms, a
17 tiny amount, the central volume 73 micrograms
18 and the steady state about a milligram. Again
19 with all kinds of possibilities in between that
20 range. Now recognizing that the central
21 concentration of 73 is only part of one adult
22 vial, and in fact conceivably it could have been
23 a whole vial at a different time point.

24 Q. Yes.

25 A. Those are the constraints
then that we can put at least in terms of maximum



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and minimum with very reasonable amounts in
between.

Now the third issue, other than
accidental or intentional administration is, can
we accept the 72? Well the issue arose really
because of the nature in which the sample was
obtained. The question that arises again
relates to a bathtub and a thimble in that the
concentrations in tissue are tremendously higher
than the concentrations in blood, or in plasma,
or serum, by factors as we have seen from the
literature three hundred fold or greater in fact.

It was thus that we questioned
whether that was a valid number, and because of
that, as you have indicated, studies were
undertaken to see if it would be possible to
mimic some of the things that happened in that
autopsy. There are two points that differ between
a study and what was done at the autopsy, that
have to be considered prior to looking at the
numbers derived.

The autopsy was done under
circumstances where no one was specifically trying
to look for digoxin by this method, it was an after
thought. The autopsy was done with a lot of



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variables that one cannot control or look for,
it was not an experiment to that extent.

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The study was done under
conditions where as best as possible people were
trying to limit what indeed could or could not
happen during that autopsy post circumstance.
So that they were trying to be careful. They
were trying to avoid getting into certain types
of pitfalls which might indeed have created
problems.

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Well, what do we know about the
results of this study? Accepting that the
circumstances were not identical and that one
can never in a controlled circumstance try to
control all the variables that go on in a clinical
circumstance where you get a call and somebody
says, oh, could you go back and do something, and
then everything that has gone on before in terms
of the variables is now basically lost. Well in
fact we have the study which Mr. Cimbura carried
out.

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THE COMMISSIONER: What is that
exhibit number?

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MR. LAMEK: The gutter blood .



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THE WITNESS: The gutter blood study.

THE COMMISSIONER: What is the exhibit number?

MR. LAMEK: The exhibit number I am just about to look for Mr. Commissioner.

MR. ROLAND: 213.

MR. LAMEK: 213, thank you.

Q. Do you have those results available to you there Doctor?

A. Yes, I do.

THE COMMISSIONER: It is not 215?

MR. LAMEK: The last document was 213 I believe.

THE COMMISSIONER: Oh 213, oh, I beg your pardon.

MR. LAMEK: Q. The very last sheet of paper in that exhibit and in particular the two right-hand columns. Yes, you were going to refer to that study I believe?

A. Yes. There are several things that are of some interest with respect to the study. One is that in a general sense, if one looks at the data, there is a tendency for comparing, for example, body fluid one samples,



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and again we don't know how well the Estrella sample really corresponds to body fluid one or body fluid two samples, we are trying to model but we have problems.

In a general sense comparing sagittal sinus to body fluid one, most of the samples in fact are increased in body fluid one samples.

Q. When you refer to body fluid one you are referring to those samples taken at the beginning of autopsy?

A. Yes, I believe so. I am not exactly sure how they separated one and two in that regard. I believe one was an earlier sample and one was then a later sample.

Q. The protocol as I understand it called for a sample to be taken at the start of autopsy and then three later?

A. Yes.

MR. ROLAND: I am showing the witness the Exhibit 213.

THE WITNESS: Oh I am sorry, my table doesn't correspond to your table and that is why I am having a problem.

MR. LAMEK: Thank you Mr. Roland.



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THE COMMISSIONER: Why would your table not correspond with ours, do you have some other document?

THE WITNESS: We have basically the same data but the column headings are different.

THE COMMISSIONER: I see.

THE WITNESS: The column headings are different.

THE COMMISSIONER: The figures are the same, are they?

THE WITNESS: Yes the figures are the same, and in addition my data contains something that this does not contain, which are the sagittal sinus samples that correspond to the same babies. Oh no, I am sorry it is here.

Q. On the left hand side.

A. The whole table is set up differently than mine, the order of all the columns is different and the headings are different. Okay. I think we are sort of back together.

Q. Okay, right.

A. I am sorry.

Q. No problem.



EE-8

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2 A. Now the general tendency is
3 examination of data, that again compared to
4 sagittal sinus, heart blood samples tend to be a
5 little bit higher and this is consonant with what
6 is in the literature in fact.

7 Furthermore, that the gutter
8 fluid samples again in a general sense tend to be
9 higher than the sagittal sinus samples.

10 Q. Yes.

11 A. So that, for example, on the
12 first one we go from a value of three to a value
13 at the start of the autopsy a value of five, or
14 later 4.4, or 4.9 up to 11 or 10. In the last
15 one number 14, 2.5 becomes 9.5.

16 There is a good deal of
17 variability in the study as one would expect from
18 this kind of study, even under the best
19 circumstances with the best of controls.

20 Q. I am sorry, when you speak
21 of variability what do you mean?

22 A. That the ratios, say
23 comparing the fluid samples to the blood samples
24 is going to be highly variable, going from 2.5 to 9
25 is about 3.8 fold, going from 3 to 5 is about 1.7
fold increase.



EE-9

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Q. Yes.

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Q. Yes.

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A. Okay. So there is bound to be variability and I would expect that in this type of experiment. Striking is that one of the samples of course is extremely high, this is the 169 sample.

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Number one is that there is a tendency towards an increase.

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Number two, that in a specific circumstance, even under controlled circumstances where you are doing an experiment and know what you are trying to do, you can get a value that is extraordinarily high.

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There is one additional patient who was studied just prior to the protocol, which I believe Dr. Phillips, or somebody has entered into evidence; I don't know if Dr. Phillips has actually appeared at this point.

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Q. Not yet.

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A. This was done just prior to the protocol and I think is another important



EE-10

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2 patient. This babe had a post mortem cardiac
3 and subclavian levels which were the same,
4 about two, and in fact the fluid level was 18,
5 which was about a nine-fold increase.

6 So we have babies that have nine-
7 fold increases; we have babies that have three-
8 fold increases; ; we have this one extraordinary
9 value of a 39-fold increase; we have other babies
10 that have two-fold increases, and three-fold and
four-fold increases.

11 What does this mean with respect
12 to how we can use the data obtained in Janice
13 Estrella?

14 In the first place this was not
15 obtained under optimal circumstances; it was not
16 obtained according to this protocol which if
17 anything decreased error. So we have a risk of
increased error and not decreased error.

18 Second, the value of of 72 if her
19 post mortem level, pre-mortem, excuse me, pre-mortem
20 level was three, with a standard multiplier type
21 of thing of two or three giving a value of six,
or perhaps a value of nine, by that mechanism
22 alone one is not surprised that one could convert
23 that nine into a 70 based on infants who have gone
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up nine-fold, other infants who have gone up
more than 30-fold, and other infants that have
gone up four-fold.



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Can we assign a probability to that?
We really can't because, again, it is impossible to exactly replicate what went on during that time. The point being that under better circumstances values of 9-fold increases and, in fact, values of 40-fold increases were achieved.

Thus, as a scientist one has to be extremely cautious about interpreting that value and say that there is a very high probability that that value may have in part or in total have been influenced by the artefactual manner in which the sample was obtained; albeit still being concerned that it might not have.

Q. Sure, yes. Yes, understood.
Dr. Speilberg, I don't know that even -- well, not even, I don't know that Mr. Cimbura carries any great brief for that number and he has said that although you could not dismiss it out of hand, which is what you are saying.

A. Precisely.

Q. Nevertheless, he couldn't have total confidence in it because of the way in which it was gathered. But I just want to be sure we are not condemning it for the wrong reason because there may be very good reasons for condemning it.



I am interested that you compare the pelvic cavity fluid levels with the sagittal sinus levels. Why do you select those? I had understood that sagittal sinus levels, if anything, tended to be rather lower than blood in peripheral circulation.

A. This is true.

Q. Is that a fair comparison?

A. This is generally true.

Although, in this other baby that we examined, again, with the variability, the heart blood level actually is the same as the subclavian level and as the femoral level and, as the femoral level, in fact, the heart blood is slightly lower than the femoral blood and yet the concentration in the body fluid is nine-fold. To give you the exact numbers ---

Q. I'm not suggesting there may not be a distortion in the cavity fluid.

A. No.

Q. But I am suggesting that to take your multiplier by reference to sagittal sinus may condemn it unduly, if you will.

A. It might. Actually, one of the things that we need from Dr. Hastreiter that I cannot get from his recent publication is, he uses --



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2 his data routinely show a three-fold increase or
3 greater but he doesn't state the site and, un-
4 fortunately, I don't know what the site was so,
5 we can't compare that.

6 Q. Well, I will try to remember to
7 ask him for you, Doctor.

8 A. It is going to be important, I
9 think, to understand that. That may help us. The
10 multipliers, as you suggest quite rightly,
11 from different sites may be different.

12 Q. Yes.

13 A. And it is certainly that way in
14 adults. In children, we don't have quite as much
15 data but the data again suggests that, for example,
16 if heart might go up three-fold, sagittal sinus might
17 go up two-fold.

18 Q. Yes.

19 A. Again, we are talking only in
20 ranges but with all the range of variability that we
21 are dealing with and, in fact, her blood level may have
22 been even higher premortem, we have to accept 72 as
23 within a very reasonable range of information obtained
24 by such mechanisms.

25 Q. Do I have your views fairly
with respect to Estrella then that you have, I think,



grave reservations about the reality of the 72 number.

A. Yes.

Q. But even if it be a real number, then applying the postmortem multiplier effect, which probably occurred to some extent and correlating that with your calculated antemortem level, it may or may not represent anything of any significance.

A. Yes.

Q. On the other hand, it may be a very real number, it may very well represent a substantial level during life.

A. I must be concerned that it might be, yes.

Q. And if it does then, once again, we are back to the same exercise that we have done with Cook, Miller, all these children.

A. Yes.

Q. You can suggest to us what different doses of what different intervals or points of time might have produced such a level.

A. Yes.

Q. And said how they got there, you cannot know, whether innocently, by accident





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2 or in some more nefarious way.

3 A. Yes.

4 Q. Can you bear with me for just
5 a moment, please?

6 A. Yes.

7 Q. Dr. Speilberg, thank you very
8 much.

9 THE COMMISSIONER: Yes. Mr. Roland?

10 EXAMINATION BY MR. ROLAND:

11 Q. Dr. Speilberg, you have told
12 us about, in some detail, the possibility of
13 medication error. In Mr. Lamek's examination
14 yesterday very briefly you told us in a general
15 sense about what the literature says about medica-
16 tion error and about the number of dosages of
17 digoxin approximately that one would see on an
18 annual basis at the Hospital for Sick Children.
19 As I recall your evidence yesterday you indicated
20 that there would be something in the neighborhood
21 of 10,000 to 15,000 doses of digoxin given annually
22 on Wards 4-A and 4-B.

23 A. Yes.

24 Q. Can you tell us, first of all,
25 about how many children on the average, or at least
in a general approximation, would be on digoxin at



any one time on 4-A and 4-B.

A. I can only give you a rough estimate from the last numbers of months data. We are actually trying to compile a somewhat larger list. On the average perhaps 15, perhaps 20 children would be receiving digoxin on a given day on the ward, somewhere in that general range, perhaps somewhat lower on some days or higher on others.

Q. So that that would be somewhere around half the children then on the wards would be on digoxin, would be receiving digoxin?

A. Roughly, that neighborhood.

Q. Yes. I gather that on the average there would be more than one dosage of digoxin given per day to the children receiving it?

A. Yes, that is true. The average child receiving maintenance therapy would receive two doses a day.

Q. Yes.

A. If a child had not previously been on digoxin and were being begun on the medicine ordinarily we would divide out what we would call the loading dose into three doses over 24 hours so that that child would receive three doses. But most of the children would receive two.



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Q. Now, what does the literature itself tell us? Is the frequency of medication error in hospitals generally -- what is the range of frequency?

A. Well, can I find some information here?

Q. Yes.

A. So that I can be a bit more accurate. It may take me a moment to find it. This information, Mr. Commissioner, is taken from a compilation, a book really looking at the literature on medication errors in a variety of hospitals, mostly in the United States, including university hospitals, tertiary care centres as well as community hospitals. I will try to bring a copy in as well as some copies of the specific chapter that we will deal with and give those to Mr. Lamek in the morning, since I wasn't aware that we would be pursuing this issue today.



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There are a number of different types of errors. The average figure quoted in a number of articles reviewed, excluding wrong time errors, which would mean, you know, a nurse administered a drug a half an hour late or something like this or a half an hour early, excluding wrong time errors, the average value given ranges anywhere from 5.5 per cent up to nearly 20 per cent of drugs being given in error.

THE COMMISSIONER: I'm sorry, you can't mean that. You mean 5 to 20, you mean one-fifth?

THE WITNESS: That's the quoted figure.

THE COMMISSIONER: Right.

THE WITNESS: Now, we have to qualify obviously what those amount to.

MR. ROLAND: Q. That's my next question.

A. We will get to those in a moment.

THE COMMISSIONER: You mean to say that for one-fifth of the time there is an error? All right.

THE WITNESS: Again, it seems quite high but not unrealistic in some ways, particularly since many of the things that we are going to be



Spielberg
ex. (Roland)

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FF2.22 talking about are not clinically significant errors.

3 MR. ROLAND: Q. Well, you have
4 told us that the range is 5.5 to 20 per cent. Can you
5 tell us what the literature in giving that range
6 defines as an error? What's the kind of errors?

7 A. There are clearly a number
8 of errors. The average figure that is quoted by
9 pharmacologists is in the range of about 10 per cent
errors.

10 Now, what that amounts to, most of
11 them are not clinically important errors, which means
12 that the patient does not suffer as a result of the
13 error. Because people include as errors, for example,
14 mixing up of two brands of antacid; Gelusil is
15 ordered and the patient received Amphigel. Now,
16 clinically, one dose of Amphigel versus Gelusil
17 probably won't make very much clinical difference,
18 certainly, but those are included as medication
errors.

19 Q. So, first of all then we
20 have the wrong drug being given?

21 A. The wrong drug being given
22 to a patient for whom a similar drug was ordered.
23 We have then errors which are much, much rarer but
24 still occur with some frequency and that frequency is
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very hard to ascertain, of patients receiving a
totally unordered medicine.

Q. Yes.

A. Now, again, a vast majority
of times that that happens nothing occurs to the
patient. Most of the time it is a medicine. For
example, if we gave Ampicillin, an antibiotic, to a
large number of normal individuals we would never
know that they received Ampicillin because no untoward
event would occur.

Similarly, even if we gave a dose
of digoxin to a substantial number of people, if the
dose were not in tremendous excess, if no clinical
consequences resulted, we would never know that it
occurred.

Other errors such as mixing up
of one medicine versus another in fact are more
frequent, particularly during times of use of vials,
and we can provide some literature on this, where
names are mixed up or misread because the vials are
similar. So, the confusion of similar types of
medicines that look the same, or pills that look the
same, are certainly not infrequent events.

How many of the maladministrations
are correct administrations --



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Q. Before you go further, you told us that it may be the wrong drug, although there was a drug that was prescribed for the patient or it may be a drug given to a patient when no drug was prescribed.

A. Right.

Q. Are there any other kinds of errors apart from that?

A. Yes, certainly.

Q. What are the other kinds?

A. Wrong amount, for example.

Q. Yes.

A. One pill was ordered, two pills were given.

Q. Yes.

A. .06cc's was ordered and .3cc's was given.

Q. Right.

A. So that these would be quantitative errors, the correct drug given to the correct patient but in an incorrect amount. Then there are errors in route. The drug is ordered intravenously and is given orally or vice versa or intramuscularly, those kinds of situations. Again, the vast majority of those things are not going to be



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2 clinically damaging to the patient. On the other
3 hand they are considered to be medication errors as
4 tabulated in these figures.

5 So, we are summing up a variety
6 of different circumstances: A wrong amount of the
7 correct drug, wrong route of the correct drug, a
8 confusion of drugs, one medication substituted for
9 another, and administration of a drug to an incorrect
patient or an incorrect drug to a patient.

10 Q. And is it all these kinds
11 of errors that are included in the statistics that
12 you have given us showing a range of 5.5 per cent to
13 20 per cent?

14 A. Yes, this includes all of
15 those errors.

16 Q. All right. Now, before we
17 go on to look at those errors in more detail. In these
18 studies was it determined that there was an error made
in the administration of the drug?

19 A. That's very important.

20 THE COMMISSIONER: Is this a
21 published study?

22 THE WITNESS: Oh, yes. We will
23 bring them all in for Mr. Lamek. Again, I wasn't
24 aware that we would be pursuing this today.
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THE COMMISSIONER: Well, I mean,
it is not one that you have made yourself?

THE WITNESS: Oh, no. I am quoting
other people's studies in the literature.

THE COMMISSIONER: Are we going to
get the study itself?

MR. ROLAND: Well, we hear it is
coming tomorrow morning, yes.

THE COMMISSIONER: Yes, all right.

THE WITNESS: Now, I'm sorry, what
was it?

MR. ROLAND: Q. In the study or
studies how is it determined that there was an error?

A. Okay. There are several
ways in which hospitals try to keep track of their
errors. One is by incident reports; in other words,
somebody recognizes that they make an error and at
the time fill out what we call an incident report
and say instead of giving one tablet of Tylenol I
gave two tablets of Tylenol to patient X.

Q. I see.

A. That actually reflects a
very small percentage of errors. The studies which
we are talking about were done in surveillance
situations where either a clinical pharmacist or



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another nurse would follow around and watch what was
going on in the wards and try to, as best as possible,
record what was happening on the ward by observing
both the order sheets, the cardexes, the way in
which samples were drawn up, et cetera, et cetera.



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2 So that this is under circumstances
3 where in fact somebody is specifically looking to
4 try to catalogue errors. If we compare incident
5 reports to errors, there is one study that quotes a ratio
6 of less than one error in a thousand as reported.
7 That seems awfully low to me, but in any case,
8 certainly only a small percentage of errors end up
9 reported, and particularly, if they end up having
10 no clinical consequence to the patient, in other
11 words, nothing immediately happens to the patient
12 and there is no unit dose system because all the
13 figures I am quoting are from non-unit dose systems,
14 then there would not be clear cut, for instance,
15 a patient's name on a syringe and you go to that
16 patient and suddenly you realize you have used his
17 syringe already on somebody else. These are all
18 non-unit dose.

19 When we are talking about unit
20 dose systems, the error rate falls dramatically into
21 the 1 per cent rate, that kind of thing, 1 to 3
22 per cent rate, which has obviously been one of the
23 reasons that we have pushed hard for unit dose at the
24 Hospital.

25 Q. So when you give us the
statistics of 5½ to 20 per cent, I take it then,



2 those studies are of non-unit dose institutions?

3 A. Yes, that is correct.

4 THE COMMISSIONER: When you are
5 talking of unit dose, you mean a dose made up for
6 each particular patient; is that what you mean?

7 THE WITNESS: Yes, these are systems
8 in which the pharmacy, upon receiving the order, will
9 pre-package a dose for a specific patient in Hospital.

10 MR. ROLAND: Q. Now, in these
11 studies, as well, do they give figures or percentages
12 of errors when the error is giving a drug to a
13 patient for which no drug was prescribed rather than
14 simply the mixing up of a drug?

15 A. This is a bit harder to
16 get at from the studies because the different studies,
17 as you see, tend to group errors in different ways.
18 The estimates that one can make is somewhere under
19 a half per cent to, in one study, as high as 3 per
20 cent. Again, that seems very high to me, but that
21 is what the study indicated. I would probably think
22 in a general sense on the lower end of the scale
23 seems more reasonable.

24 Q. And I take it these studies
25 are calculated on doses, are they, doses of drugs
given, not on patients?



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A. Yes, that is correct.

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Q. So when we are talking about

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half a per cent to 3 per cent, that is of the total
number of doses given in a specific period of time?

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A. Yes, correct.

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Q. I see. So that if we applied,

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then, that range of a half a per cent or under a
half a per cent to 3 per cent to the number of annual
doses given, as you have estimated, at the

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Hospital for Sick Children, how many doses
do we get in which at least, based on the literature,
it may be thought that digoxin was given to a baby
who was not prescribed digoxin?

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A. If we use simply those

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figures, we come out in the neighbourhood of perhaps

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50 incorrect doses a year. Now, the caveat again

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that one must add is that we are not sure whether the

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error rate is uniform across all medicine, and it

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probably is not. It probably would be higher for

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some of the more trivial medicines and it may also

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be dependent on a specific ward. For example,

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digoxin is a very frequently used drug on the

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Cardiology Ward. That might influence the relative

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number of errors being used, particularly if most

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of the patients or a large majority of the patients

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2 are on the drug at a given time.

4 3 Q. And when you say it is a
4 familiar drug and that might influence it, how do
5 you think that would influence it?

6 A. Well, it might in several
7 different ways. If people were very familiar with
8 the drug, it might, to a certain extent, tend to
9 decrease the errors. On the other hand, if it is
10 being used in an awful lot of patients on the ward
11 and one is administering drugs to a tremendous number
12 of patients on the ward in a rapid fashion, then it
13 might increase the rate. Thus, I really cannot say
14 what influence it would have. It could go either
15 way.

16 THE COMMISSIONER: And what you are
17 saying is that 50 doses of digoxin per year roughly,
18 this is what you are saying, would be given to a baby
19 who is not prescribed digoxin; is that what you are
20 saying?

21 THE WITNESS: I would say that is
22 sort of the upper bounds and beyond that in terms
23 of lower bounds, I do not know.

24 MR. ROLAND: To be clear, Mr.
25 Commissioner, of course we are not saying that that
happened at the Hospital for Sick Children. We are



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2 saying if you extrapolate from the literature, that
3 is the possible figure.

4 THE COMMISSIONER: I understand
5 that. I am a little shocked by this information, that
6 is all. Fifty instances of giving babies -- I am
7 not saying that this happens, it is possible, but it
8 does seem odd that that would be what happens.

9 MR. ROLAND: Well, Mr. Commissioner,
10 the Hospital believes that it is important to put
11 all the information before you, and this is from the
12 literature. We want you to have this information.

13 THE COMMISSIONER: Yes, I understand
14 that. When I say I am shocked, I just do not believe
15 it, that is all. I would like to read this document.

16 MR. ROLAND: Well, I see it is
17 4:30.

18 THE COMMISSIONER: Perhaps I will
19 get that chance tomorrow.

20 MR. ROLAND: Perhaps this would be
21 a good time to adjourn until tomorrow and we can
22 present that to you first thing in the morning.

23 THE COMMISSIONER: Yes, all right.
24 Maybe I will be in a better position to accept it
25 then. Yes, all right, until 10 o'clock tomorrow.

MS. CRONK: Excuse me, Mr.



Commissioner, before we leave, if it would be possible to obtain an estimate of time if counsel are in a position to give it.

THE COMMISSIONER: We are worried about time again. Mr. Roland, can you tell us how long you will be?

MR. ROLAND: I think maybe half to three-quarters of an hour. Maybe a little longer.

THE COMMISSIONER: Mr. Brown?

MR. BROWN: I do not anticipate being very long.

THE COMMISSIONER: You will not be?

MR. BROWN: Do not anticipate being very long.

THE COMMISSIONER: What does that mean, 15 minutes or less?

MR. BROWN: 15, 20, 25 minutes at the most.

THE COMMISSIONER: Mr. Strathy.

MR. STRATHY: An hour or less.

MR. HUNT: Half an hour.

MS. MCINTYRE: 15 minutes.

MS. CRONK: That is fine, sir.

MS. JACKMAN: 15 minutes.

THE COMMISSIONER: I think it will



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certainly keep us going all day tomorrow.

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MS. CRONK: Thank you, sir.

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THE COMMISSIONER: Yes, all right.

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---Whereupon the hearing adjourned until 10:00 a.m.
Wednesday, the 26th day of October, 1983.

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